(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 April 2002 (25.04.2002)

PCT

(10) International Publication Number
WO 02/32896 A1

(51) **International Patent Classification**[7]: **C07D 413/04**, 413/14, A61K 31/4192, 31/4245, 31/443, 31/4439, 31/496, 31/5355, 31/55, A61P 3/10, 25/18, 25/24, 25/28

(21) **International Application Number:** PCT/DK01/00676

(22) **International Filing Date:** 12 October 2001 (12.10.2001)

(25) **Filing Language:** English

(26) **Publication Language:** English

(30) **Priority Data:**

PA 2000 01537	16 October 2000 (16.10.2000)	DK
60/242,409	20 October 2000 (20.10.2000)	US

(71) **Applicant** *(for all designated States except US)*: **NOVO NORDISK A/S** [DK/DK]; Corporate Patents, Novo Allé, DK-2880 Bagsværd (DK).

(72) **Inventors; and**

(75) **Inventors/Applicants** *(for US only)*: **OLESEN, Preben, Houlberg** [DK/DK]; Ørevadsvej 20, DK-2400 Copenhagen NV (DK). **KURTZHALS, Peter** [DK/DK]; Bygaden 61 B, DK-2630 Taastrup (DK). **WORSAAE, Helle** [DK/DK]; Skovmosevej 21, DK-2820 Gentofte (DK). **HANSEN, Bo, Falck** [DK/DK]; Grønnevej 131 B, DK-2830 Virum (DK). **SØRENSEN, Anders, Robert** [DK/DK]; Hyldemorsvej 1B, DK-2730 Herlev (DK). **BOWLER, Andrew, Neil** [GB/DK]; Gammel Hareskovvej 333, 1, DK-3500 Værløse (DK).

(74) **Common Representative: NOVO NORDISK A/S**; Corporate Patents, Novo Allé, DK-2880 Bagsværd (DK).

(81) **Designated States** *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) **Designated States** *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/32896 A1

(54) **Title:** FURAZANYL-TRIAZOLE DERIVATES FOR THE TREATMENT OF DISEASES

(57) **Abstract:** Pharmaceutical compositions comprising 1-(furazanyl-3-yl)-[1,2,3]triazole derivatives of the general formula (I) wherein the meanings of R^1, R^2, R^3, R^4, R^5 and n are as given in the description, for the treatment and/or prevention of disorders and diseases, wherein an inhibition of GSK-3 (glycogen synthase kinase-3) is beneficial, especially Alzheimer's disease, bipolar disorder, IGT (impaired glucose tolerance), Type 1 diabetes, Type 2 diabetes and obesity.

FURAZANYL-TRIAZOLE DERIVATES FOR THE TREATMENT OF DISEASES

FIELD OF THE INVENTION

The present invention relates to pharmaceutical compositions comprising 1-(furazan-3-yl)-[1,2,3]triazole derivatives for the treatment and/or prevention of disorders and diseases, wherein an inhibition of GSK-3 (glycogen synthase kinase-3) is beneficial, especially Alzheimer's disease, bipolar disorder, IGT (impaired glucose tolerance), Type 1 diabetes, Type 2 diabetes and obesity.

BACKGROUND OF THE INVENTION

GSK-3 is a protein-serine kinase implicated in the hormonal control of several regulatory proteins. It was first discovered by virtue of its ability to phosphorylate and inactivate glycogen synthase, the regulatory enzyme of glycogen synthesis in mammals (Embi, N. et al. (1980), EUR J BIOCHEM *107*, 519-527; Rylatt, D. B. et al. (1980), EUR J BIOCHEM *107*, 529-537). Since then a number of other substrates have been identified, implicating the enzyme in the regulation of several physiological processes.

GSK-3 exists in two isoforms, termed GSK-3α and GSK-3β, which are derived from distinct genes and show 85% sequence identity. Unlike many protein kinases, both GSK-3 isoforms are constitutively active in resting cells, and are primarily regulated by inactivation. Thus, it has been shown that GSK-3 is inhibited by serine phosphorylation in response to insulin and growth factors such as IGF-1 and EGF via activation of the MAP kinase cascade or via PI3 kinase dependent activation of protein kinase B.

Compounds that inhibit GSK-3 activity are useful in the treatment of diseases, disorders and conditions, wherein such an inhibition is beneficial, eg in diseases, disorders and conditions related to GSK-3, in diseases, disorders and conditions related to a dysfunction of GSK-3, in diseases, disorders and conditions in which growth factor induced inhibition of GSK-3 is insufficient and in diseases, disorders and conditions in which glycogen synthase is insufficiently activated.

Type 1 diabetes, also known as insulin dependent diabetes mellitus (IDDM), is caused by an autoimmune destruction of insulin producing cells in the pancreas, leading to a lack of insulin. Thus, individuals with Type 1 diabetes require daily injections of the hormone to sustain life. Current methods of insulin administration, however, cannot reproduce the normal β cell's ability to precisely control blood glucose and other metabolic variables. Hence, the Type 1

diabetic remains susceptible to the long-term and devastating complications of diabetes, such as cardiovascular disease, retinopathy, nephropathy and neuropathy.

Type 2 diabetes, also known as non-insulin dependent diabetes mellitus (NIDDM), is the most common of all metabolic disorders and poses a major health problem worldwide. Type 2 diabetes results from defects in both insulin secretion and insulin action, but the exact underlying mechanism(s) causing the disease are not known. An elevation of hepatic glucose production contributes significantly to causing fasting hyperglycemia, whereas decreased insulin-mediated glucose uptake by muscle and fat is a major contributor to postprandial hyperglycemia. Moreover, the metabolic fate of glucose taken up by muscle is not normal in people with Type 2 diabetes. For example muscle glycogen synthase activity and glycogen synthesis have been shown to be impaired in Type 2 diabetes. The available treatments do not allow for a complete normalisation of the metabolic state and some of them are associated with side effects. The metabolic derangements created by hyperglycemia, together with the strong association between Type 2 diabetes, obesity, hypertension and hyperlipidemia, lead to an extensive list of long-term complications, including a high rate of cardiovascular death due to accelerated atherosclerosis, as well as typical complications of diabetes such as retinopathy, nephropathy and neuropathy.

Thus, there is still a need for novel approaches to treat diabetes.

Recently, it has been found that GSK-3 expression is elevated in muscle of people with Type 2 diabetes and that the GSK-3 expression is inversely correlated with both glycogen synthase activity and glucose disposal. Thus, an increased GSK-3 expression may contribute to the impaired glycogen synthase activity and insulin resistance that occurs in Type 2 diabetes. Other recent experiments have suggested a role for GSK-3 in attenuating insulin action via its phosphorylation of insulin receptor substrate 1.

Recent studies using lithium salts also support the notion that inhibition of GSK-3 would be beneficial in the treatment of diabetes. It has been known for a long time that lithium has a stimulatory effect on glucose metabolism, most prominently on glycogen synthesis. Treatment with lithium salts has also been shown to alleviate the diabetic state in both Type 1 and Type 2 diabetic patients. The molecular mechanism for these effects of lithium has until recently been unknown. However, it has now been found that lithium inhibits GSK-3. Although lithium might also have effects on other molecular targets than GSK-3, this finding contributes to explain the molecular effects of lithium and supports that inhibition of GSK-3 leading

to activation of glycogen synthase has significant effect on stimulation of glucose metabolism.

In conclusion, GSK-3 inhibitors may be useful for the treatment of metabolic disorders, such as IGT, Type 1 diabetes and Type 2 diabetes.

GSK-3 is also involved in biological pathways relating to Alzheimer's disease and GSK-3 inhibitors may be useful in the treatment thereof. Alzheimer's disease is characterized histopathologically by the presence of intraneuronal neurofibrillary tangles and the extracellular deposition of β amyloid in the brain, especially the hippocampus. The neurofibrillary tangles are made up of paired helical filaments (PHFs), the major protein subunit of which is the abnormally phosphorylated and glycosylated microtubule associated protein tau (τ). In the tangle bearing neurons in Alzheimer's disease, the normal cytoskeleton is disrupted and replaced with PHFs. GSK-3 is one of several kinases that phosphorylates tau in vitro on the abnormal sites characteristic of PHF-tau and has also been demonstrated to do this in living cells. Furthermore, the GSK-3 inhibitor lithium blocks tau hyperphosphorylation in cells. Further evidence for a role of GSK-3 in Alzheimer's disease is provided by ia (i) the association of GSK-3 with presenellin 1, (ii) reduced cytotoxicity of β amyloid protein in neuronal cells incubated with GSK-3 antisense and (iii) 50% increased expression of GSK-3 in postsynaptic supernatants of Alzheimer's disease compared to normal brain tissue.

Lithium has been used for decades in the treatment of manic depression (bipolar disorder). The mechanism of action of lithium as a mood-stabilizing agent remains unknown, although effects on biological membranes and synaptic neurotransmission have been suggested. However, GSK-3 activity could be implicated in the etiology of bipolar disorder. One mechanism by which lithium and other GSK-3 inhibitors may act to treat bipolar disorder is to increase the survival of neurons subjected to aberrantly high levels of excitation induced by the neurotransmitter glutamate. Glutamate may also be implicated in mediating neurodegeneration following acute damage, eg in cerebral ischemia, traumatic brain injury and bacterial, viral and prion infection. Excessive glutamate signalling has also been implicated in the chronic neuronal damage seen in diseases such as Huntington's chorea, Parkinson's disease, amyotrophic lateral sclerosis and multiple sclerosis. Consequently, GSK-3 inhibitors may be useful in the treatment of these and other neurodegenerative disorders. In connection with this it should be noted that lithium has a variety of biological effects that, if mediated

through the inhibition of GSK-3, could provide an even broader application of GSK-3 inhibitors.

Furthermore, GSK-3 has been shown to phosphorylate the transcription factor NF-AT, which participates in the activation of early immune response genes. Phosphorylation prevents translocation of NF-AT to the nucleus and thus blocks early immune responses. Thus, GSK-3 inhibitors may prolong and potentiate the immunostimulatory effect of certain cytokines and such an effect could be beneficial in the use of cytokines for cancer or immunotherapy.

WO 98/16528 discloses purine derivates, which are stated to be effective as GSK-3 inhibitors. WO 99/65897 discloses pyrimidine and pyridine derivates, which are stated to be effective as GSK-3 inhibitors. Furthermore, WO 00/21927 discloses 3-amino-4-maleimide derivatives, which are stated to be effective as GSK-3 inhibitors. WO 00/38675 discloses a method for the treatment and/or prophylaxis of conditions associated with a need for the inhibition of GSK-3 comprising the administration of different groups of known compounds, ia bisindole maleimide derivatives, indole aryl maleimides and indolocarbazole derivatives. These compounds differ structurally from the present compounds.

Some of the compounds of the general formula (I) are commercially available from SPECS and BioSPECS, B. V. Flemінglaan 16, 2289 CP Rijswijk, The Netherlands. However, no uses have been disclosed or suggested for these compounds.

In view of the art's interest in GSK-3 inhibitors and the great potential thereof, the identification of potent and specific GSK-3 inhibitors would be a highly desirable contribution to the art. The present invention provides such a contribution to the art being based on the finding that the 1-(furazan-3-yl)-[1,2,3]triazole derivatives derivatives of the general formula (I) potently and specifically inhibit GSK-3.

The present compounds are accordingly useful in the treatment and/or prevention of a wide range of conditions and disorders in which an inhibition of GSK-3 is beneficial.

DEFINITIONS

The following is a detailed definition of the terms used to describe the present compounds.

"Halogen" designates an atom selected from the group consisting of F, Cl, Br and I.

The term "C_{1-6}-alkyl" in the present context designates a saturated, branched or straight hydrocarbon group having from 1 to 6 carbon atoms. Representative examples include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, n-pentyl, isopentyl, neopentyl, *tert*-pentyl, n-hexyl, isohexyl and the like.

The term "C_{1-6}-alkoxy" in the present context designates a group –O-C_{1-6}-alkyl, wherein C_{1-6}-alkyl is as defined above. Representative examples include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, butoxy, isobutoxy, *sec*-butoxy, *tert*-butoxy, n-pentoxy, isopentoxy, neopentoxy, *tert*-pentoxy, n-hexoxy, isohexoxy and the like.

The term "C_{1-6}-alkoxycarbonyl" in the present context designates a group –C(O)O-C_{1-6}-alkyl, wherein C_{1-6}-alkyl is as defined above. Representative examples include, but are not limited to, methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, *sec*-butoxycarbonyl, *tert*-butoxycarbonyl, n-pentoxycarbonyl, isopentoxycarbonyl, neopentoxycarbonyl, *tert*-pentoxycarbonyl, n-hexoxycarbonyl, isohexoxycarbonyl and the like.

The term "C_{2-6}-alkenyl" as used herein represents a branched or straight hydrocarbon group having from 2 to 6 carbon atoms and at least one double bond. Examples of such groups include, but are not limited to, vinyl, 1-propenyl, 2-propenyl, isopropenyl, 1,3-butadienyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl and the like.

The term "C_{2-6}-alkynyl" as used herein represents a branched or straight hydrocarbon group having from 2 to 6 carbon atoms and at least one triple bond. Examples of such groups include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 3-hexynyl, 5-hexynyl, 2,4-hexadiynyl and the like.

The term "C_{3-8}-cycloalkyl" as used herein represents a saturated carbocyclic group having from 3 to 8 carbon atoms. Representative examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and the like.

The term "C_{3-8}-heterocyclyl" as used herein represents a saturated 3 to 8 membered ring containing one or more heteroatoms selected from nitrogen, oxygen and sulfur. Representative ex-

amples are pyrrolidinyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, aziridinyl, tetrahydrofuranyl and the like.

The term "aryl" as used herein represents a carbocyclic aromatic ring system such as phenyl, biphenyl, naphthyl, anthracenyl, phenanthrenyl, fluorenyl, indenyl, pentalenyl, azulenyl, biphenylenyl and the like. Aryl is also intended to include the partially hydrogenated derivatives of the carbocyclic aromatic systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 1,2,3,4-tetrahydronaphthyl, 1,4-dihydronaphthyl and the like.

The term "heteroaryl" as used herein represents a heterocyclic aromatic ring system containing one or more heteroatoms selected from nitrogen, oxygen and sulfur such as furanyl, thiophenyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, isoxazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5- triazinyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, tetrazolyl, thiadiazinyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, indazolyl, benzimidazolyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, purinyl, quinazolinyl, quinolizinyl, quinolinyl, isoquinolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, azepinyl, diazepinyl, acridinyl and the like. Heteroaryl is also intended to include the partially hydrogenated derivatives of the heterocyclic systems enumerated above. Non-limiting examples of such partially hydrogenated derivatives are 2,3-dihydrobenzofuranyl, pyrrolinyl, pyrazolinyl, indolinyl, oxazolidinyl, oxazolinyl, oxazepinyl and the like.

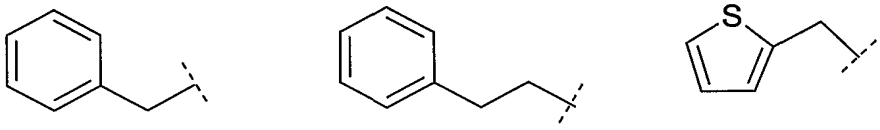
The term "heteroarylamino" as used herein represents a group –NH-heteroaryl, wherein heteroaryl has the above meaning.

The term "3 to 14 membered, mono-, bi- or tricyclic carbocyclic ring system" as used herein represents a carbocyclic ring system which may optionally contain one or more double bonds. Representative examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopententyl, cyclohexenyl, cycloheptyl, cyclooctyl, phenyl, biphenyl, naphthyl, anthracenyl, phenanthrenyl, fluorenyl, indenyl, pentalenyl, azulenyl, biphenylenyl, 1,2,3,4-tetrahydronaphthyl, 1,4-dihydronaphthyl and the like.

The term "3 to 7 membered, saturated heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur" intends to include eg perhy-

droazepinyl, piperidinyl, morpholinyl, pyrrolidinyl, piperazinyl, aziridinyl and the like. When it is annelated with aryl or heteroaryl representative examples are 2,3-dihydroindolyl, 1,3-dihydroisoindolyl and the like.

"Aryl-C_{1-6}-alkyl", "heteroaryl-C_{1-6}-alkyl" etc. means C_{1-6}-alkyl as defined above, substituted by an aryl or heteroaryl as defined above, for example:

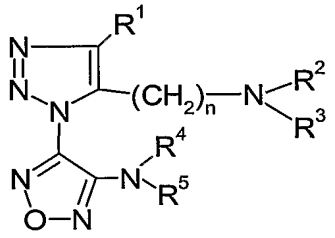


Certain of the above defined terms may occur more than once in the structural formulae, and upon such occurrence each term shall be defined independently of the other.

The term "GSK-3" as used herein is intended to mean GSK-3α and/or GSK-β.

DETAILED DESCRIPTION OF THE INVENTION

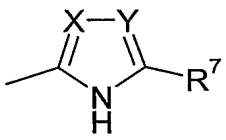
The invention relates to a pharmaceutical composition comprising, as an active ingredient, at least one compound of the general formula (I):



(I)

wherein

R^1 is –CN, -C(=O)NR^6R^7, -C(=O)NH-NR^6R^7, –C(=O)NH-N=CR^6R^7, –C(=O)OR^7, –CR^6=N-NH-C(=O)R^7 or



,

X and Y independently are =C- or =N(R^6)-,

R^6 is hydrogen or C_{1-6}-alkyl,

R^7 is hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-cycloalkyl, C_{3-8}-heterocyclyl, aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, heteroarylamino-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-heterocyclyl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, heteroaryl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-heterocyclyl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl-C_{2-6}-alkynyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl or C_{3-8}-heterocyclyl-C_{2-6}-alkynyl,

- wherein the cyclic moieties optionally may be substituted with one to three substituents independently selected from halogen, nitro, cyano, oxo, trifluoromethyl, hydroxy, C_{1-6}-alkoxy, carboxy, C_{1-6}-alkoxycarbonyl, C_{1-6}-alkyl, $-NR^8R^9$, -S-C_{1-6}-alkyl, -S(=O)-C_{1-6}-alkyl, -S(=O)$_2$-C_{1-6}-alkyl and -S(=O)$_2$$NR^8R^9$, wherein R^8 and R^9 independently are hydrogen or C_{1-6}-alkyl, or with two substituents in adjacent positions together forming a $-O-(CH_2)_m-O-$ radical, wherein m is 1 or 2,

or R^6 and R^7, when attached to the same carbon atom, together with the said carbon atom may form a mono-, bi- or tricyclic, 3 to 14 membered ring system, which is optionally substituted with one to three substituents independently selected from halogen, nitro, cyano, oxo, trifluoromethyl, hydroxy, C_{1-6}-alkoxy, carboxy, C_{1-6}-alkoxycarbonyl, C_{1-6}-alkyl, $-NR^8R^9$, -S-C_{1-6}-alkyl, -S(=O)-C_{1-6}-alkyl, -S(=O)$_2$-C_{1-6}-alkyl and -S(=O)$_2$$NR^8R^9$, wherein R^8 and R^9 independently are hydrogen or C_{1-6}-alkyl,

n is 1 or 2,

R^2 and R^3 independently are hydrogen, C_{1-6}-alkyl, aryl, heteroaryl, aryl-C_{1-6}-alkyl or heteroaryl-C_{1-6}-alkyl, or R^2 and R^3 together with the nitrogen atom to which they are attached form a 3 to 7 membered, heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, which ring may optionally be annelated with aryl or heteroaryl,

- wherein the cyclic moieties optionally may be substituted with one to three substituents independently selected from halogen, nitro, cyano, oxo, trifluoromethyl, hydroxy, C_{1-6}-alkoxy, carboxy, C_{1-6}-alkoxycarbonyl, C_{1-6}-alkyl, C_{1-6}-alkyl substituted with hydroxy, $-NR^{10}R^{11}$, -S-C_{1-6}-alkyl, -S(=O)-C_{1-6}-alkyl, -S(=O)$_2$-C_{1-6}-alkyl and -S(=O)$_2$$NR^{10}R^{11}$, wherein R^{10} and R^{11} independently are hydrogen or C_{1-6}-alkyl, and

R^4 and R^5 independently are hydrogen or C_{1-6}-alkyl, or R^4 and R^5 together with the nitrogen atom to which they are attached form a 3 to 7 membered, heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur,

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof,

together with one or more pharmaceutically acceptable carriers or excipients.

In one embodiment, R^1 is $-C(=O)NH-N=CR^6R^7$, wherein R^6 is as defined for formula (I), and R^7 is C_{1-6}-alkyl, C_{2-6}-alkenyl, aryl, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, heteroaryl or heteroaryl-C_{1-6}-alkyl, wherein the cyclic moieties may optionally be substituted as defined for formula (I).

In another embodiment, R^7 is pyridyl, 1-benzotriazolylmethyl, phenyl or furanyl, which may optionally be substituted with one to three substituents selected from C_{1-6}-alkoxy, hydroxy, C_{1-6}-alkyl, halogen and nitro or with two substituents in adjacent positions together forming a $-O-(CH_2)_m-O-$ radical, wherein m is 1 or 2.

In yet another embodiment, R^7 is pyridyl.

In still another embodiment, R^7 is phenyl, which may optionally be substituted with one to three substituents selected from C_{1-6}-alkoxy, hydroxy, C_{1-6}-alkyl, halogen and nitro or with two substituents in adjacent positions together forming a $-O-(CH_2)_m-O-$ radical, wherein m is 1 or 2.

In a further embodiment, R^1 is $-C(=O)NH-N=CR^6R^7$, wherein R^6 and R^7 together form 1,2,3,4-tetrahydronaphthyl or 9,10-dihydroanthracenyl, which may optionally be substituted with one to three substituents selected from C_{1-6}-alkoxy, hydroxy, oxo, C_{1-6}-alkyl, halogen and nitro.

In still a further embodiment, R^1 is $-C(=O)OR^7$, wherein R^7 is hydrogen, C_{1-6}-alkyl or heteroaryl-C_{1-6}-alkyl, wherein the heteroaryl moiety may optionally be substituted as defined for formula (I).

In yet a further embodiment, R^1 is $-C(=O)OR^7$, wherein R^7 is C_{1-6}-alkyl or pyridyl-C_{1-6}-alkyl.

In another embodiment, R^1 is $-C(=O)NR^6R^7$, wherein R^6 and R^7 are as defined for formula (I).

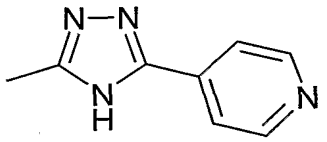
In still another embodiment, R^1 is $-C(=O)NR^6R^7$, wherein R^6 is as defined for formula (I), and R^7 is heteroaryl-C_{1-6}-alkyl, heteroarylamino-C_{1-6}-alkyl or aryl-C_{1-6}-alkyl, which may optionally be substituted as defined for formula (I).

In still another embodiment, R^1 is $-C(=O)NR^6R^7$, wherein R^6 is as defined for formula (I), and R^7 is pyridyl-C_{1-6}-alkyl, imidazolyl-C_{1-6}-alkyl, indolyl-C_{1-6}-alkyl, pyridylamino-C_{1-6}-alkyl or phenyl-C_{1-6}-alkyl, which may optionally be substituted as defined for formula (I).

In still a further embodiment, R^1 is $-C(=O)NR^6R^7$, wherein R^6 is as defined for formula (I), and R^7 is pyridyl-C_{1-6}-alkyl, imidazolyl-C_{1-6}-alkyl, indolyl-C_{1-6}-alkyl, pyridylamino-C_{1-6}-alkyl or phenyl-C_{1-6}-alkyl, wherein the cyclic moieties may optionally be substituted with one to three substituents selected from halogen, nitro, hydroxy, and $-S(=O)_2NH_2$.

In another embodiment, R^1 is $-C(=O)-NH-NH_2$.

In yet another embodiment, R^1 is



.

In still another embodiment, n is 1.

In still another embodiment, R^2 and R^3 independently are selected from hydrogen, C_{1-6}-alkyl, aryl-C_{1-6}-alkyl, aryl, heteroaryl-C_{1-6}-alkyl and C_{3-8}-cycloalkyl, wherein the cyclic moieties may optionally be substituted as defined for formula (I).

In still a further embodiment, R^2 and R^3 independently are selected from hydrogen, C_{1-6}-alkyl, phenyl-C_{1-6}-alkyl, phenyl, pyridyl-C_{1-6}-alkyl and C_{3-8}-cycloalkyl, wherein the cyclic moieties optionally may be substituted with one to three substituents selected from C_{1-6}-alkyl, oxo, nitro, C_{1-6}-alkoxycarbonyl and C_{1-6}-alkyl substituted with hydroxy.

In another embodiment, R^2 and R^3 are both C_{1-6}-alkyl.

In a further embodiment, R^2 and R^3 together with the nitrogen atom to which they are attached form a ring system selected from 1-perhydroazepinyl, 1-piperidinyl, 1-morpholinyl, 1,2,3,4-tetrahydroquinolin-1-yl, 1-pyrrolidinyl, 1-piperazinyl, 2,3-dihydroindol-1-yl, 1-benzotriazol-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl and 1,2,4-triazol-1-yl, which may optionally be substituted as defined for formula (I).

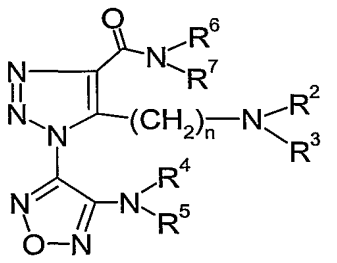
In still a further embodiment, R^2 and R^3 together with the nitrogen atom to which they are attached form a ring system selected from 1-perhydroazepinyl, 1-piperidinyl, 1-pyrrolidinyl and 1-morpholinyl, which may optionally be substituted with one to three substituents selected from C_{1-6}-alkyl, oxo, nitro, C_{1-6}-alkoxycarbonyl and C_{1-6}-alkyl substituted with hydroxy.

In yet a further embodiment, R^2 and R^3 together with the nitrogen atom to which they are attached form a ring selected from 1-perhydroazepinyl, 1-piperidinyl, 1-pyrrolidinyl and 1-morpholinyl.

In another embodiment, R^4 and R^5 are both hydrogen.

In yet another embodiment, the pharmaceutical composition is in unit dosage form and comprises from about 0.05 mg to about 1000 mg, preferably from about 0.1 mg to about 500 mg and especially preferred from about 0.5 mg to about 200 mg of the compound of the general formula (I) or an optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

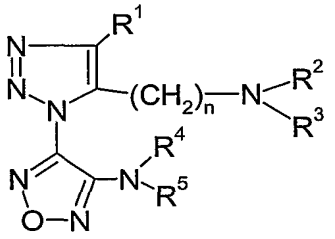
In another aspect, the invention relates to a compound of the general formula (I'):



(I')

wherein n and R^2 to R^7 are as defined for formula (I) or in any one of the above embodiments, as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

In another aspect, the invention relates to a pharmaceutical composition comprising, as an active ingredient, at least one compound of the general formula (II):



(II)

wherein

R^1 is –CN, -C(=O)NR^6R^7, -C(=O)NH-NR^6R^7, –C(=O)NH-N=CR^6R^7, –C(=O)OR^7 *or* –CR^6=N-NH-C(=O)R^7,

wherein

R^6 is hydrogen or C_{1-6}-alkyl,

R^7 is hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-cycloalkyl, C_{3-8}-heterocyclyl, aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-heterocyclyl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, heteroaryl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-heterocyclyl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl-C_{2-6}-alkynyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl or C_{3-8}-heterocyclyl-C_{2-6}-alkynyl,

- wherein the cyclic moieties optionally may be substituted with one to three substituents independently selected from halogen, nitro, cyano, oxo, trifluoromethyl, hydroxy, C_{1-6}-alkoxy, carboxy, C_{1-6}-alkoxycarbonyl, C_{1-6}-alkyl, –NR^8R^9, -S-C_{1-6}-alkyl, -S(=O)-C_{1-6}-alkyl, -$S(=O)_2$-C_{1-6}-alkyl and -$S(=O)_2NR^8R^9$, wherein R^8 and R^9 independently are hydrogen or C_{1-6}-alkyl, or with two substituents in adjacent positions together forming a –O-$(CH_2)_m$-O- radical, wherein m is 1 or 2, and

or R^6 and R^7, when attached to the same carbon atom, together with the said carbon atom may form a mono-, bi- or tricyclic, 3 to 14 membered ring system, which is optionally substituted with one to three substituents independently selected from halogen, nitro, cyano, oxo, trifluoromethyl, hydroxy, C_{1-6}-alkoxy, carboxy, C_{1-6}-alkoxycarbonyl, C_{1-6}-alkyl, –NR^8R^9,

-S-C_{1-6}-alkyl, -S(=O)-C_{1-6}-alkyl, -S(=O)$_2$-C_{1-6}-alkyl and -S(=O)$_2$NR^8R^9, wherein R^8 and R^9 independently are hydrogen or C_{1-6}-alkyl,

n is 1 or 2,

R^2 and R^3 independently are hydrogen, C_{1-6}-alkyl, aryl, heteroaryl, aryl-C_{1-6}-alkyl or heteroaryl-C_{1-6}-alkyl, or R^2 and R^3 together with the nitrogen atom to which they are attached form a 3 to 7 membered, heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, which ring may optionally be annelated with aryl or heteroaryl,

- wherein the cyclic moieties optionally may be substituted with one to three substituents independently selected from halogen, nitro, cyano, oxo, trifluoromethyl, hydroxy, C_{1-6}-alkoxy, carboxy, C_{1-6}-alkoxycarbonyl, C_{1-6}-alkyl, C_{1-6}-alkyl substituted with hydroxy, –N$R^{10}R^{11}$, -S-C_{1-6}-alkyl, -S(=O)-C_{1-6}-alkyl, -S(=O)$_2$-C_{1-6}-alkyl and -S(=O)$_2$N$R^{10}R^{11}$, wherein R^{10} and R^{11} independently are hydrogen or C_{1-6}-alkyl, and

R^4 and R^5 independently are hydrogen or C_{1-6}-alkyl, or R^4 and R^5 together with the nitrogen atom to which they are attached form a 3 to 7 membered, heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur,

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof,

together with one or more pharmaceutically acceptable carriers or excipients.

In one embodiment, R^1 is –C(=O)NH-N=CR^6R^7, wherein R^7 is aryl, heteroaryl or heteroaryl-C_{1-6}-alkyl, wherein the cyclic moieties may optionally be substituted as defined for formula (I). Preferably, R^7 is pyridyl, 1-benzotriazolylmethyl, phenyl or furanyl, which may optionally be substituted with one to three substituents selected from C_{1-6}-alkoxy, hydroxy, oxo, C_{1-6}-alkyl, halogen and nitro or with two substituents in adjacent positions together forming a –O-$(CH_2)_m$-O- radical, wherein m is 1 or 2. More preferably, R^7 is pyridyl, which is unsubstituted, or R^7 is phenyl, which may optionally be substituted with one to three substituents selected from C_{1-6}-alkoxy, hydroxy, C_{1-6}-alkyl, halogen and nitro or with two substituents in adjacent positions together forming a –O-$(CH_2)_m$-O- radical, wherein m is 1 or 2.

In another embodiment, R^1 is $-C(=O)NH-N=CR^6R^7$, wherein R^6 and R^7 together form 1,2,3,4-tetrahydronaphthyl or 9,10-dihydroanthracenyl, which may optionally be substituted with one to three substituents selected from C_{1-6}-alkoxy, hydroxy, oxo, C_{1-6}-alkyl, halogen and nitro.

In yet another embodiment, R^1 is $-C(=O)OR^7$, wherein R^7 is C_{1-6}-alkyl.

In still another embodiment, R^1 is $-C(=O)NR^6R^7$, wherein R^6 and R^7 are as defined for formula (II). Preferably, R^6 is hydrogen and R^7 is heteroaryl-C_{1-6}-alkyl or aryl-C_{1-6}-alkyl, which may be substituted as defined for formula (II).

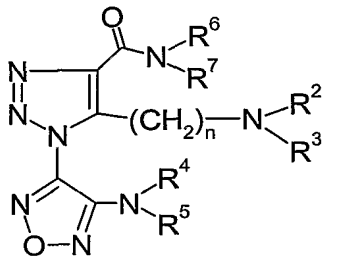
In another embodiment, n is 1.

In another embodiment, R^2 and R^3 are independently selected from C_{1-6}-alkyl, aryl-C_{1-6}-alkyl, aryl and C_{3-8}-cycloalkyl, wherein the cyclic moieties may optionally be substituted as defined for formula (II). More preferably, R^2 and R^3 are independently selected from C_{1-6}-alkyl, phenyl-C_{1-6}-alkyl, phenyl and C_{3-8}-cycloalkyl, wherein the cyclic moieties optionally may be substituted with one to three substituents selected from C_{1-6}-alkyl, oxo, nitro, C_{1-6}-alkoxycarbonyl and C_{1-6}-alkyl substituted with hydroxy. Even more preferably, R^2 and R^3 are both C_{1-6}-alkyl.

In still another embodiment, R^2 and R^3 together with the nitrogen atom to which they are attached form a ring system selected from 1-perhydroazepinyl, 1-piperidinyl, 1-morpholinyl, 1,2,3,4-tetrahydroquinolin-1-yl, 1-pyrrolidinyl, 1-piperazinyl, 2,3-dihydroindol-1-yl, 1-benzotriazol-1-yl, 1,2,3,4-tetrahydroisoquinolin-2-yl and 1,2,4-triazol-1-yl, which may optionally be substituted as for formula (II). Preferably, R^2 and R^3 together with the nitrogen atom to which they are attached form a ring system selected from 1-perhydroazepinyl, 1-piperidinyl, 1-pyrrolidinyl and 1-morpholinyl, which may optionally be substituted with one to three substituents selected from C_{1-6}-alkyl, oxo, nitro, C_{1-6}-alkoxycarbonyl and C_{1-6}-alkyl substituted with hydroxy. More preferably, R^2 and R^3 together with the nitrogen atom to which they are attached form a ring selected from 1-perhydroazepinyl, 1-piperidinyl, 1-pyrrolidinyl and 1-morpholinyl.

In another embodiment, R^4 and R^5 are both hydrogen.

In another aspect, the invention relates to a compound of the general formula (II'):



(II')

wherein n and R^2 to R^7 are as defined for formula (II) or in any one of the above embodiments, as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

The compounds of the present invention may have one or more asymmetric centres and it is intended that any optical isomers, as separated, pure or partially purified optical isomers or racemic mixtures thereof are included within the scope of the invention.

Furthermore, when a double bond or a fully or partially saturated ring system is present in the molecule geometric isomers may be formed. It is intended that any geometric isomers, as separated, pure or partially purified geometric isomers or mixtures thereof are included within the scope of the invention. Likewise, molecules having a bond with restricted rotation may form geometric isomers. These are also intended to be included within the scope of the present invention.

Furthermore, some of the compounds of the present invention may exist in different tautomeric forms and it is intended that any tautomeric forms, which the compounds are able to form, are included within the scope of the present invention.

The present invention also encompasses pharmaceutically acceptable salts of the present compounds. Such salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids. Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, nitric acids and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methanesulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic,

benzenesulfonic, p-toluenesulfonic acids and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977, 66, 2, which is incorporated herein by reference. Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like. Examples of ammonium and alkylated ammonium salts include ammonium, methylammonium, dimethylammonium, trimethylammonium, ethylammonium, hydroxyethylammonium, diethylammonium, butylammonium, tetramethylammonium salts and the like.

Also intended as pharmaceutically acceptable acid addition salts are the hydrates, which the present compounds are able to form.

The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent.

The compounds of the present invention may form solvates with standard low molecular weight solvents using methods well known to the person skilled in the art. Such solvates are also contemplated as being within the scope of the present invention.

The invention also encompasses prodrugs of the present compounds, which on administration undergo chemical conversion by metabolic processes before becoming active pharmacological substances. In general, such prodrugs will be functional derivatives of the present compounds, which are readily convertible in vivo into the required compound of the formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The invention also encompasses active metabolites of the present compounds.

The present compounds inhibit GSK-3 and accordingly they may find use in the treatment and/or delaying or prevention of the progression of hyperglycemia, dyslipidemia, Type 1 diabetes, Type 2 diabetes, hypertriglyceridemia, syndrome X, insulin resistance, IGT, obesity, diabetes as a consequence of obesity, diabetic dyslipidemia, hyperlipidemia, cardiovascular diseases and hypertension. Furthermore, they may find use in the treatment and/or delaying or prevention of the progression of appetite regulation and energy expenditure disorders

such as eating disorders eg bulimia, and other conditions, wherein a weight reduction is required.

They may also find use in the treatment and/or delaying or prevention of the progression of bipolar disorder (manic depressive syndrome), mania, Alzheimer's disease, bipolar disorder, Huntington's chorea, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, leukopenia, anxiety, movement disorder, aggression, psychosis, seizures, panic attacks, hysteria or sleep disorders. Furthermore, they may be useful as contraceptives, cf WO 97/41854, and for the treatment of cancer, hair-loss and neurotraumatic diseases, such as acute stroke, cf WO 00/21927.

In an embodiment of the invention, the present compounds are used for the manufacture of a pharmaceutical composition for the treatment and/or delaying or prevention of the progression of diseases, disorders and conditions related to GSK-3.

In a further embodiment of the invention, the present compounds are used for the manufacture of a pharmaceutical composition for the treatment and/or delaying or prevention of the progression of diseases, disorders and conditions, wherein growth factor induced inhibition of GSK-3 is insufficient.

In another embodiment of the invention, the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or delaying or prevention of the progression of diseases, disorders and conditions, wherein glycogen metabolism exhibits abnormalities.

In another embodiment of the invention, the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or delaying or prevention of the progression of diseases, disorders and conditions, wherein glycogen synthase is insufficiently activated.

In yet another embodiment of the invention, the present compounds are used for the preparation of a pharmaceutical composition for the lowering of blood glucose, both in the fasting and postprandial stage.

In a further embodiment of the invention, the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or delaying or prevention of the

progression of diseases, disorders and conditions involving elevated blood glucose, both elevated fasting and postprandial blood glucose.

In still a further embodiment of the invention, the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or delaying or prevention of the progression of hyperglycemia.

In yet an aspect of the invention, the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or delaying or prevention of the progression of IGT.

In another aspect of the invention, the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or delaying or prevention of the progression of Type 2 diabetes.

In still another aspect of the invention, the present compounds are used for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from IGT to Type 2 diabetes.

In yet another aspect of the invention, the present compounds are used for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes.

In a further aspect of the invention, the present compounds are used for the preparation of a pharmaceutical composition for the treatment and/or delaying or prevention of the progression of Type 1 diabetes. Such treatment and/or delaying or prevention are normally accompanied by insulin therapy.

In another aspect of the invention, the present compounds may be used for the preparation of a pharmaceutical composition for the treatment and/or delaying or prevention of the progression of Alzheimer's disease.

In another aspect of the invention, the present compounds may be used for the preparation of a pharmaceutical composition for the treatment and/or delaying or prevention of the progression of bipolar disorder.

Furthermore, the present compounds may be used for the preparation of a pharmaceutical composition for the treatment and/or delaying or prevention of the progression of obesity.

The present compounds may also be used for the preparation of a pharmaceutical composition for the treatment and/or delaying or prevention of the progression of an appetite regulation or energy expenditure disorder such as an eating disorder eg bulimia or binge eating.

In a further aspect of the invention, the present compounds may be administered in combination with one or more further pharmacologically active substances eg selected from antidiabetic agents, antiobesity agents, antihypertensive agents, agents for the treatment and/or prevention of complications resulting from or associated with diabetes, agents for the treatment of Alzheimer's disease and agents for the treatment of bipolar disorder.

Thus, in one embodiment of the invention, the present compounds are administered in combination with one or more further antidiabetic agents.

Suitable antidiabetic agents comprise insulin, GLP-1 derivatives such as those disclosed in WO 98/08871 (Novo Nordisk A/S), which is incorporated herein by reference as well as orally active hypoglycemic agents.

The orally active hypoglycemic agents preferably comprise sulfonylureas, biguanides, meglitinides, oxadiazolidinediones, thiazolidinediones, glucosidase inhibitors, glucagon antagonists such as those disclosed in WO 99/01423 and WO 00/39088 (Novo Nordisk A/S) and Agouron Pharmaceuticals, Inc., GLP-1 agonists, potassium channel openers such as those disclosed in WO 97/26265 and WO 99/03861 (Novo Nordisk A/S) which are incorporated herein by reference, insulin sensitizers, DPP-IV inhibitors, PTPase inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis and/or glycogenolysis, glucose uptake modulators, compounds modifying the lipid metabolism such as antihyperlipidemic agents and antilipidemic agents, compounds lowering food intake, PPAR and RXR agonists and agents acting on the ATP-dependent potassium channel of the β-cells.

In another embodiment of the invention, the present compounds are administered in combination with insulin.

In a further embodiment the present compounds are administered in combination with a sulfonylurea eg tolbutamide, glibenclamide, glipizide or glicazide.

In another embodiment the present compounds are administered in combination with a biguanide eg metformin.

In yet another embodiment the present compounds are administered in combination with a meglitinide eg repaglinide.

In still another embodiment the present compounds are administered in combination with a thiazolidinedione eg troglitazone, ciglitazone, pioglitazone, rosiglitazone or the compounds disclosed in WO 97/41097 (Dr. Reddy's Research Foundation).

Furthermore, the present compounds may be administered in combination with the insulin sensitizers disclosed in WO 99/19313 (Dr. Reddy's Research Foundation).

In a further embodiment the present compounds are administered in combination with an α-glucosidase inhibitor eg miglitol or acarbose.

In another embodiment the present compounds are administered in combination with an agent acting on the ATP-dependent potassium channel of the β-cells eg tolbutamide, glibenclamide, glipizide, glicazide or repaglinide.

Furthermore, the present compounds may be administered in combination with nateglinide.

In still another embodiment the present compounds are administered in combination with an antihyperlipidemic agent or antilipidemic agent eg cholestyramine, colestipol, clofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, probucol or dextrothyroxine.

In a further embodiment the present compounds are administered in combination with more than one of the above-mentioned compounds eg in combination with a sulfonylurea and metformin, a sulfonylurea and acarbose, repaglinide and metformin, insulin and a sulfonylurea, insulin and metformin, insulin and troglitazone, insulin and lovastatin, etc.

Furthermore, the present compounds may be administered in combination with one or more antiobesity agents or appetite regulating agents.

Such agents may be selected from the group consisting of CART (cocaine amphetamine regulated transcript) agonists, NPY (neuropeptide Y) antagonists, MC4 agonists, orexin antagonists, H3 antagonists, TNF (tumor necrosis factor) agonists, CRF (corticotropin releasing factor) agonists, CRF BP (corticotropin releasing factor binding protein) antagonists, urocortin agonists, β3 agonists, MSH (melanocyte-stimulating hormone) agonists, MCH (melanocyte-concentrating hormone) antagonists, CCK agonists, serotonin re-uptake inhibitors, mixed serotonin and noradrenergic compounds, 5HT agonists, bombesin agonists, galanin antagonists, growth hormone, growth hormone releasing compounds, TRH agonists, UCP (uncoupling protein) 2 or 3 modulators, leptin agonists, DA agonists (bromocriptin, doprexin), lipase/amylase inhibitors, PPAR modulators, RXR modulators or TR β agonists.

In one embodiment of the invention, the antiobesity agent is leptin.

In another embodiment the antiobesity agent is dexamphetamine or amphetamine.

In another embodiment the antiobesity agent is fenfluramine or dexfenfluramine.

In still another embodiment the antiobesity agent is sibutramine.

In a further embodiment the antiobesity agent is orlistat.

In another embodiment the antiobesity agent is mazindol or phentermine.

Furthermore, the present compounds may be administered in combination with one or more antihypertensive agents. Examples of antihypertensive agents are β-blockers such as alprenolol, atenolol, timolol, pindolol, propranolol and metoprolol, ACE (angiotensin converting enzyme) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril and ramipril, calcium channel blockers such as nifedipine, felodipine, nicardipine, isradipine, nimodipine, diltiazem and verapamil, and α-blockers such as doxazosin, urapidil, prazosin and terazosin. Further reference can be made to Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

Furthermore, the present compounds may be administered in combination with one or more agents for the treatment of Alzheimer's disease. Examples of such agents are tacrine, donepezil, haloperidol, olanzapine, quetiapine, risperidone, alprazolam, buspirone, diazepam, lorazepam, amitriptyline, bupropion, desipramine, fluoxetine, fluvoxamine, nefazodone, nortriptyline, paroxetine, sertraline and trazodone.

The present compounds may also be administered in combination with one or more agents for the treatment of bipolar disorder. Examples of such agents are lithium, valproate, divalproex, carbamazepine, antipsychotic drugs such as haloperidol and perphenazine, antianxiety agents such as lorazepam and clonazepam, antidepressants such as bupropion, fluoxetine, fluvoxamine, paroxetine, sertraline, mirtazepine, phenelzine, tranylcypromine, nefazodone, amitriptyline, desipramine, imipramine, nortriptyline and venlafaxine.

It should be understood that any suitable combination of the present compounds with one or more of the above-mentioned compounds and optionally one or more further pharmacologically active substances are considered to be within the scope of the present invention.

PHARMACEUTICAL COMPOSITIONS

The present compounds may be administered alone or in combination with pharmaceutically acceptable carriers or excipients, in either single or multiple doses. The pharmaceutical compositions according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

The pharmaceutical compositions may be specifically formulated for administration by any suitable route such as the oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), transdermal, intracisternal, intraperitoneal, vaginal and parenteral (including subcutaneous, intramuscular, intrathecal, intravenous and intradermal) route, the oral route being preferred. It will be appreciated that the preferred route will depend on the general condition and age of the subject to be treated, the nature of the condition to be treated and the active ingredient chosen.

Pharmaceutical compositions for oral administration include solid dosage forms such as capsules, tablets, dragees, pills, lozenges, powders and granules. Where appropriate, they can be prepared with coatings such as enteric coatings or they can be formulated so as to pro-

vide controlled release of the active ingredient such as sustained or prolonged release according to methods well known in the art.

Liquid dosage forms for oral administration include solutions, emulsions, suspensions, syrups and elixirs.

Pharmaceutical compositions for parenteral administration include sterile aqueous and non-aqueous injectable solutions, dispersions, suspensions or emulsions as well as sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use. Depot injectable formulations are also contemplated as being within the scope of the present invention.

Other suitable administration forms include suppositories, sprays, ointments, cremes, gels, inhalants, dermal patches, implants etc.

A typical oral dosage is in the range of from about 0.001 to about 100 mg/kg body weight per day, preferably from about 0.01 to about 50 mg/kg body weight per day, and more preferred from about 0.05 to about 10 mg/kg body weight per day administered in one or more dosages such as 1 to 3 dosages. The exact dosage will depend upon the frequency and mode of administration, the sex, age, weight and general condition of the subject treated, the nature and severity of the condition treated and any concomitant diseases to be treated and other factors evident to those skilled in the art.

The formulations may conveniently be presented in unit dosage form by methods known to those skilled in the art. A typical unit dosage form for oral administration one or more times per day such as 1 to 3 times per day may contain of from 0.05 to about 1000 mg, preferably from about 0.1 to about 500 mg, and more preferred from about 0.5 mg to about 200 mg.

For parenteral routes, such as intravenous, intrathecal, intramuscular and similar administration, typically doses are in the order of about half the dose employed for oral administration.

The present compounds are generally utilized as the free substance or as a pharmaceutically acceptable salt thereof. One example is an acid addition salt of a compound having the utility of a free base. When a compound of the formula (I) contains a free base such salts are prepared in a conventional manner by treating a solution or suspension of a free base of the formula (I) with a chemical equivalent of a pharmaceutically acceptable acid, for example, inorganic and

organic acids. Representative examples are mentioned above. Physiologically acceptable salts of a compound with a hydroxy group include the anion of said compound in combination with a suitable cation such as sodium or ammonium ion.

For parenteral administration, solutions of the compounds of the formula (I) in sterile aqueous solution, aqueous propylene glycol or sesame or peanut oil may be employed. Such aqueous solutions should be suitable buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. The aqueous solutions are particularly suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents. Examples of solid carriers are lactose, terra alba, sucrose, cyclodextrin, talc, gelatine, agar, pectin, acacia, magnesium stearate, stearic acid or lower alkyl ethers of cellulose. Examples of liquid carriers are syrup, peanut oil, olive oil, phospholipids, fatty acids, fatty acid amines, polyoxyethylene or water. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The pharmaceutical compositions formed by combining the compounds of the formula (I) and the pharmaceutically acceptable carriers are then readily administered in a variety of dosage forms suitable for the disclosed routes of administration. The formulations may conveniently be presented in unit dosage form by methods known in the art of pharmacy.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules or tablets, each containing a predetermined amount of the active ingredient, and which may include a suitable excipient. These formulations may be in the form of powder or granules, as a solution or suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion.

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatine capsule in powder or pellet form or it can be in the form of a troche or lozenge. The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatine capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

A typical tablet, which may be prepared by conventional tabletting techniques, may contain:

Core:		
Active compound (as free compound or salt thereof)		5.0 mg
Lactosum Ph. Eur.		67.8 mg
Cellulose, microcryst. (Avicel)		31.4 mg
Amberlite® IRP88*		1.0 mg
Magnesii stearas Ph. Eur.		q.s.
Coating:		
Hydroxypropyl methylcellulose	approx.	9 mg
Mywacett 9-40 T**	approx.	0.9 mg

* Polacrillin potassium NF, tablet disintegrant, Rohm and Haas.

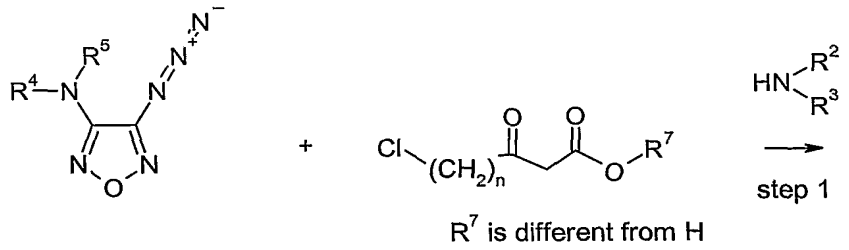
** Acylated monoglyceride used as plasticizer for film coating.

If desired, the pharmaceutical composition of the invention may comprise the compound of the formula (I) in combination with further pharmacologically active substances such as those described in the foregoing.

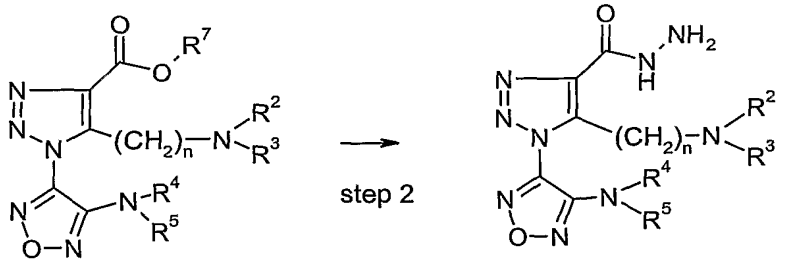
The present invention is further illustrated by the following representative examples which are, however, not intended to limit the scope of the invention in any way.

EXAMPLES

General procedure (A) for the preparation of compounds of the formulae (Ia) to (If), wherein n, R^2, R^3, R^4, R^5, R^6 and R^7 are as defined for formula (I):

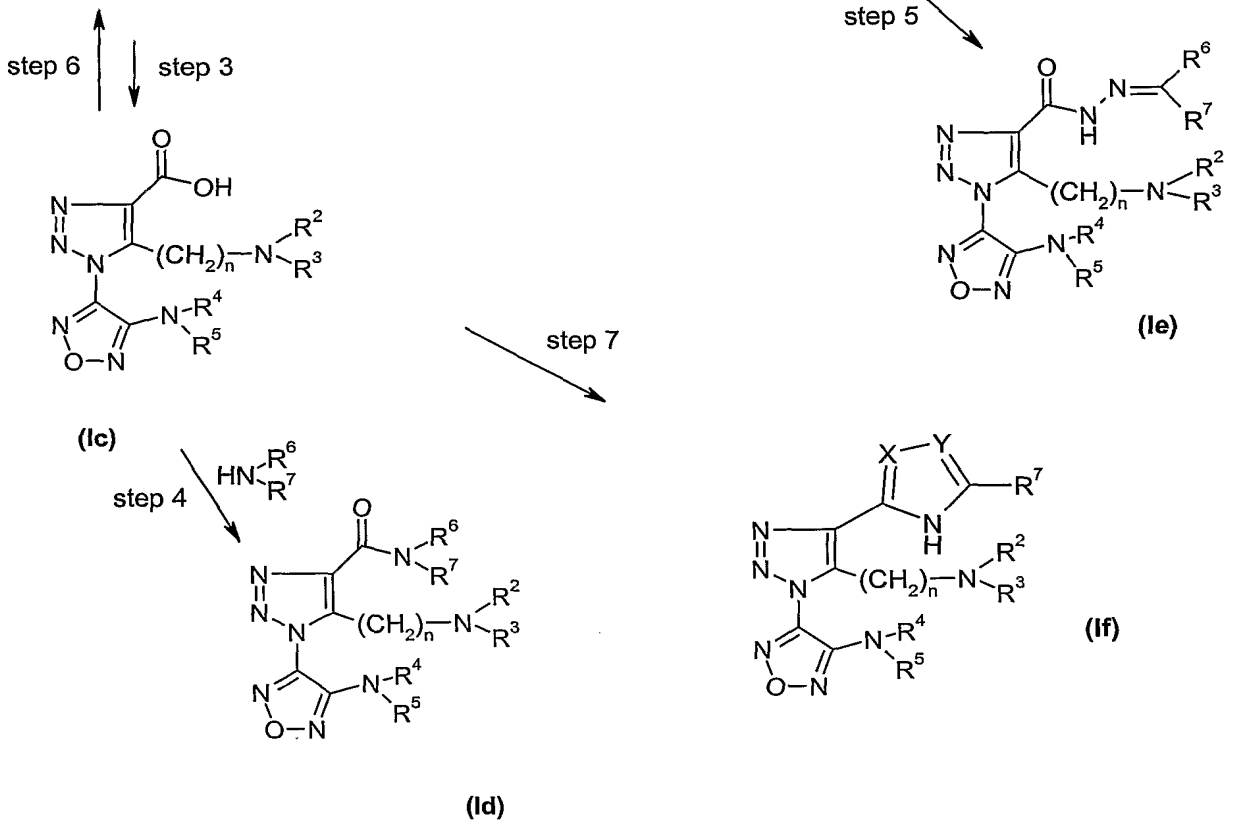


R^7 is different from H



(Ia), R^7 is different from H

(Ib)



(Ic)

(Id)

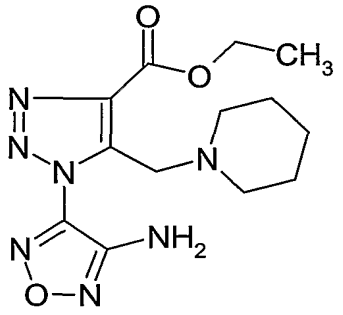
(Ie)

(If)

The general procedure is illustrated in the following examples.

Example 1 (general procedure (A), step 1)

1-(4-Aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid ethyl ester

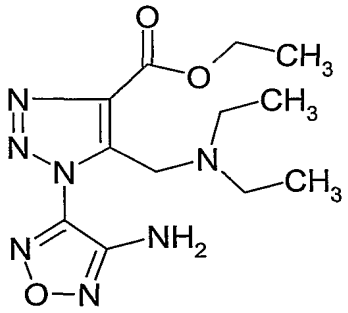


To a solution of 3-amino-4-azidofurazane (10 mmol, 1.26 g) (Tselinskii, I. V.; Mel'nikova, S. F.; Vergizov, S. N.; J.Org.Chem.USSR (Engl. Transl.); 17; 5; 1981; 994-995) in ethanol (30 ml), ethyl 4-chloroacetoacetate (15.0 mmol, 2.46 g) and piperidine (30 mmol, 2.55 g) were added. The reaction mixture was stirred overnight at room temperature, and then heated at reflux for 2 hours. After cooling, the reaction mixture was evaporated to 5 ml volume and water (100 ml) was added. The water phase was extracted with ether (2 x 75 ml). The ether phase was extracted with 1N hydrochloric acid solution (3 x 50 ml). The hydrochloric acid extracts were collected and made alkaline with a 30% ammonium hydroxide solution. The title compound separated as an oil and was extracted with ether (3 x 50 ml). The ether extracts were dried over magnesium sulphate and evaporated. The crude compound was triturated with hexane, and the crystalline compound was filtered giving the title compound in 750 mg yield. Mp 123-124 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45-1.5 (m, 9H), 2.40-2.50 (m, 4H), 4.15 (s, 2H), 4.40-4.50 (q, 2H), 5.35 (s, 2H).

Example 2 (general procedure (A), step 1)

1-(4-Aminofurazan-3-yl)-5-diethylaminomethyl-1*H*-[1,2,3]triazole-4-carboxylic acid ethyl ester

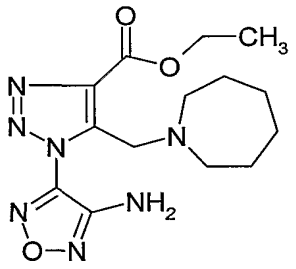


The title compound was prepared in exactly the same manner as example 1 starting from 3-amino-4-azidofurazan from ethyl 4-chloroacetoacetate and diethylamine. Mp 97-100 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.85-1.95 (t, 6H), 1.40-1.50 (t, 3H), 2.40-2.55 (q, 4H), 4.22 (s, 2H), 4.40-4.55 (q, 2H), 5.13 (s, 2H).

Example 3 (general procedure (A), step 1)

1-(4-Aminofurazan-3-yl)-5-azepan-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid ethyl ester

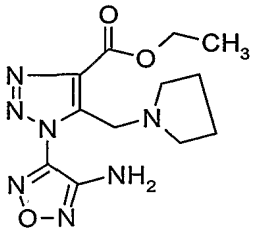


The title compound was prepared in exactly the same manner as example 1 starting from 3-amino-4-azidofurazane and ethyl 4-chloroacetoacetate and hexamethyleneimine. Mp 104-105 °C.

^{1}H NMR $CDCl_3$: δ 1.45 (m, 11H), 2.60 (m, 4H), 4.30 (s, 2H), 4.50 (q, 2H), 5.15 (s, 2H).

Example 4 (general procedure (A), step 1)

1-(4-Aminofurazan-3-yl)-5-pyrrolidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid ethyl ester

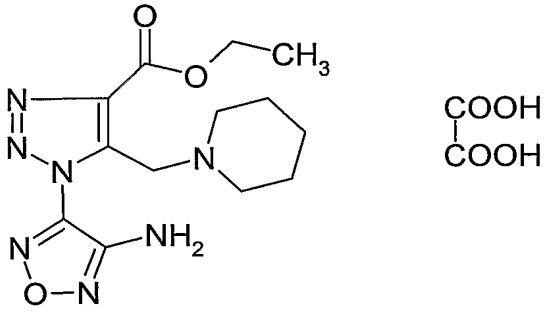


The title compound was prepared in exactly the same manner as example 1 starting from 3-amino-4-azidofurazan and ethyl 4-chloroacetoacetate and pyrrolidine. Mp 157-158 °C.

^{1}H NMR $CDCl_3$: δ 1.45 (t, 3H), 1.72 (m, 4H), 2.10 (m, 4H), 4.22 (s, 2H), 4.45 (q, 2H) 5.45 (s, 2H).

Example 5

1-(4-Aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid ethyl ester oxalate

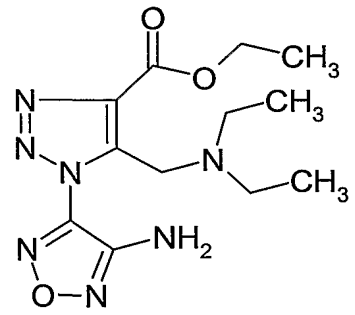


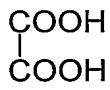
To a solution of 1-(4-aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid ethyl ester (0.3 mmol, 95 mg) in acetone (5 ml) oxalic acid (0.33 mmol, 30 mg) was added. Ether (5 ml) was added and the mixture was left overnight. The precipitated compound was filtered, giving the title compound in 70 mg yield. Mp 192-194 °C.

^{1}H NMR (300 MHz, DMSO): δ 1.10-1.25 (m, 6H), 1.25-1.35 (t, 3H), 2.20-2.30 (m, 4H), 4.05 (s, 2H), 4.40-4.45 (q, 2H), 6.65 (s, 2H).

Example 6

1-(4-Aminofurazan-3-yl)-5-diethylaminomethyl-1*H*-[1,2,3]triazole-4-carboxylic acid ethyl ester oxalate



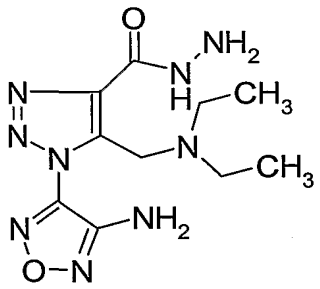


The title compound was prepared in exactly the same way as example 5. Mp 155-156 °C.

^{1}H NMR (300 MHz, DMSO): δ 0.70-0.80 (t, 6H, J = 7 Hz), 1.30-1.40 (t, 3H), 2.25-2.40 (q, 4H, J = 7 Hz), 4.05 (s, 2H), 4.35-4.50 (q, 2H), 6.10 (s, 2H).

Example 7 (general procedure (A), step 2)

1-(4-Aminofurazan-3-yl)-5-diethylaminomethyl-1*H*-[1,2,3]triazole-4-carboxylic acid hydrazide

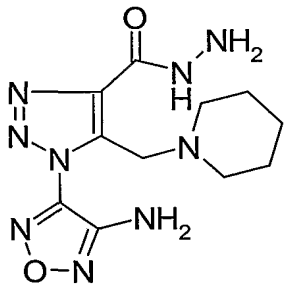


To a solution of 1-(4-aminofurazan-3-yl)-5-diethylaminomethyl-1*H*-[1,2,3]triazole-4-carboxylic acid ethyl ester oxalate (2.5 mmol, 1.0 g) in ethanol (30 ml) hydrazine hydrate (5 ml) was added. The reaction mixture was stirred at room temperature for 2 hours, and then evaporated to half the volume. Water (50 ml) was added and the precipitated compound was filtered washed with water and dried. The title compound was obtained in 700 mg yield. Mp 173-174 °C.

^{1}H NMR (300 MHz, DMSO): δ 0.70-0.80 (t, 6H, J = 7 Hz), 2.25-2.40 (q, 4H, J = 7 Hz), 4.00 (s, 2H), 4.55 (s, 2H), 6.15 (s, 2H), 10.10 (s, 1H.)

Example 8 (general procedure (A), step 2)

1-(4-Aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid hydrazide

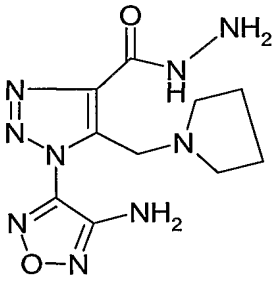


The title compound was prepared in exactly the same way as example 7 starting from 1-(4-aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid ethyl ester and hydrazine hydrate. Mp 181-182 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40-1.60 (m, 6H), 2.45-2.55 (m, 4H), 4.05 (s, 2H) 4.15 (s, 2H), 5.40 (s, 2H), 9.80 (s, 1H).

Example 9 (general procedure (A), step 2)

1-(4-Aminofurazan-3-yl)-5-pyrrolidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid hydrazide

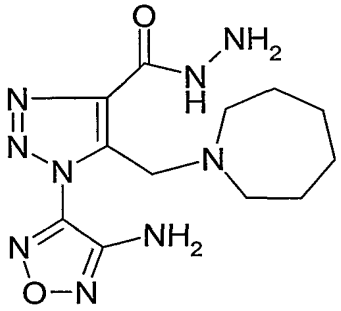


The title compound was prepared in exactly the same manner as example 7 starting from 1-(4-aminofurazan-3-yl)-5-pyrrolidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid ethyl ester and hydrazine hydrate. Mp 212–213 °C.

^{1}H NMR DMSO: δ 1.50 (m, 4H), 2.32 (m, 4H), 4.15 (s, 2H), 4.55 (s, 2H), 6.65 (s, 2H), 10.0 (s, 1H).

Example 10 (general procedure (A), step 2)

1-(4-Aminofurazan-3-yl)-5-azepan-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid hydrazide

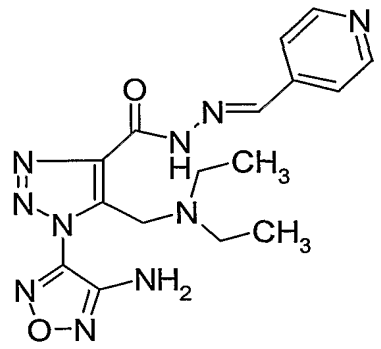


The title compound was prepared in exactly the same manner as example 7 starting from 1-(4-aminofurazan-3-yl)-5-azepan-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid ethyl ester and hydrazine hydrate. Mp 171-173 °C.

^{1}H NMR DMSO: δ 1.35 (m, 8H), 2.40 (m, 4H), 4.15 (s, 2H), 4.55 (s, 2H), 6.65 (s, 2H), 10.0 (s, 1H).

Example 11 (general procedure (A), step 5)

1-(4-Aminofurazan-3-yl)-5-diethylaminomethyl-1*H*-[1,2,3]triazole-4-carboxylic acid pyridin-4-ylmethylene hydrazide

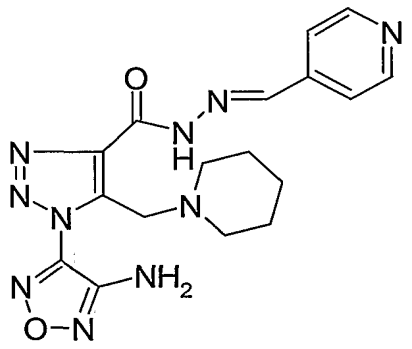


To a solution of 1-(4-aminofurazan-3-yl)-5-diethylaminomethyl-1*H*-[1,2,3]triazole-4-carboxylic acid hydrazide (730 mg, 2.5 mmol) in ethanol (30 ml) 4-pyridinecarboxaldehyde (294 mg, 2.75 mmol) was added. The reaction mixture was heated at reflux for 1 hour. The reaction mixture was evaporated, and ether (30 ml) was added. The crystalline compound was filtered, washed with ether and dried. The title compound was obtained in 650 mg yield. Mp 188-189 °C.

^{1}H NMR (300 MHz, DMSO): δ0.70-0.80 (t, 6H, J = 7 Hz), 2.25-2.40 (q, 4H, J = 7 Hz), 4.10 (s, 2H), 6.70 (s, 2H), 7.56-7.70 (d, 2H), 8.60 (s, 1H), 8.65-8.70 (d, 2H), 12.70 (s, 1H).

Example 12 (general procedure (A), step 5)

1-(4-Aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid pyridin-4-ylmethylene hydrazide

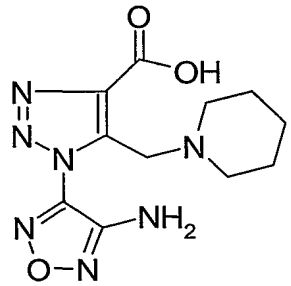


The title compound was prepared in exactly the same manner as example 11 starting from 1-(4-aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid hydrazide and 4-pyridinecarboxaldehyde. Mp 173-174 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ1.45-1.5 (m, 6H), 2.40-2.50 (m, 4H), 4.15 (s, 2H), 6.2 (s, 2H), 7.65 (d, 2H), 8.55 (s, 1H), 8.63 (d, 2H), 12.45 (s, 1H).

Example 13 (general procedure (A), step 3)

1-(4-Aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid hydrochloride

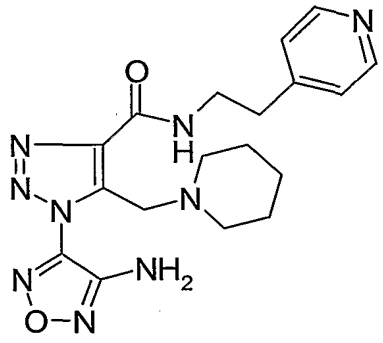


A solution of 1-(4-aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid ethyl ester (321 mg, 1 mmol) in 20 ml 1N hydrochloric acid was heated at reflux for 8 hours. The solution was evaporated to dryness and triturated with acetone. The crystalline

compound was filtered and dried. The title compound was obtained in 250 mg yield. Mp 199-200 °C.

^{1}H NMR (300 MHz, DMSO): δ 1.44-1.55 (m, 2H), 1.60-1.80 (m, 4H), 3.1-3.3 (m, 4H), 4.25 (s, 2H), 6.7 (s, 2H), 10.8 (s, br, 1H).

Example 14 (general procedure (A), step 4)
1-(4-Aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid (2-pyridin-4-ylethyl)amide dioxalate

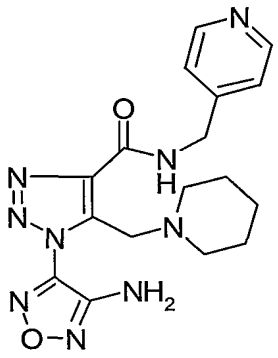


To a solution of 1-(4-aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid (100 mg, 0.33 mmol) in DMF (*N,N*-dimethylformamide) (10 ml) 1-hydroxybenzotriazole hydrate (45 mg, 0.33 mmol) and *N*-ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide hydrochloride (77 mg, 0.5 mmol) were added. The reaction mixture was stirred at room temperature for 0.5 hours and then 4-(2-aminoethyl)pyridine (61.0 mg, 0.5 mmol) was added. The reaction mixture was stirred at room temperature for 2 hours and then water (50 ml) was added. The water phase was extracted with ether (2 x 50 ml). The organic extracts were dried over magnesium sulphate and evaporated. The crude compound was crystallised as the dioxalate salt from acetone. Yield 85 mg. Mp 161-163 °C.

1H NMR (300 MHz, DMSO): δ 1.10-1.20 (m, 6H), 2.15- 2.30 (m, 4H), 2.85-2.95 (t, 2H), 3.45-3.55 (m, 2H), 4.02 (s, 2H), 6.15 (s, 2H), 7.30 (d, 2H), 8.45 (d, 2H), 9.0 (t, 1H).

Example 15 (general procedure (A), step 4)

1-(4-Aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid (pyridin-4-ylmethyl)amide

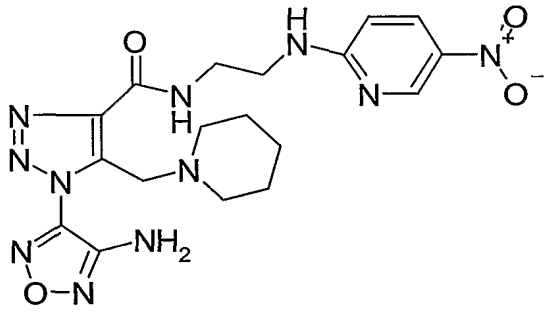


The title compound was prepared in exactly the same manner as example 14 starting from 1-(4-aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid and 4-(aminomethyl)pyridine. Mp 219-221 °C.

^{1}H NMR $CDCl_3$: δ 1.45 (m, 6H), 2.45 (m, 4H), 4.15 (s, 2H), 4.65 (d,2H), 5.45 (s, 2H), 7.25 (d, 2H), 8.55 (d, 2H), 8.70 (t,1H).

Example 16 (general procedure (A), step 4)

1-(4-Aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid [2-(5-nitro-pyridin-2-ylamino)ethyl]amide oxalate.

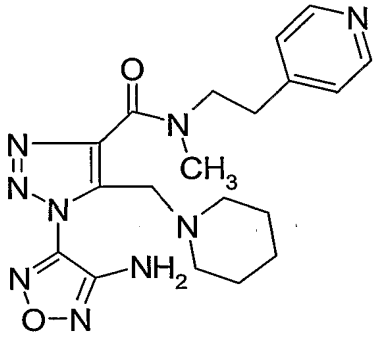


The title compound was prepared in exactly the same manner as example 14 starting from 1-(4-aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid and 2-(2-aminoethylamino)-5-nitropyridinepyridine. The free base was precipitated as the oxalate salt from 2-propanol. Mp 179-182 °C.

^{1}H NMR DMSO: δ 1.23 (m, 6H), 2.35 (m, 4H), 3.40-3.70 (m, 4H), 4.05 (s, 2H), 6.55 (d,2H, br), 6.20 (s, 1H, br), 8.10 (d, 1H), 8.23 (s, 1H, br), 8.90 (d,1H), 9.10 (d, 1H).

Example 17 (general procedure (A), step 4)

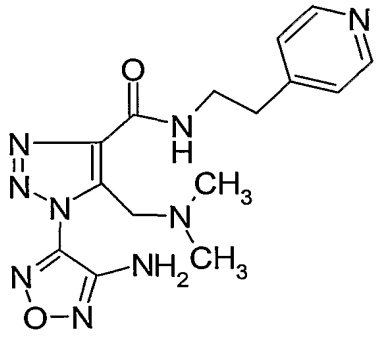
1-(4-Aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid methyl-(2-pyridin-4-ylethyl)amide dioxalate.



The title compound was prepared in exactly the same manner as example 14 starting from 1-(4-aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid and 4-(2-methylamino)ethyl)pyridine. The free base was precipitated as the dioxalate salt from acetone. Mp 163-168 °C.

Example 18 (general procedure (A), step 4)

1-(4-Aminofurazan-3-yl)-5-dimethylaminomethyl-1*H*-[1,2,3]triazole-4-carboxylic acid (2-pyridin-4-ylethyl)amide dioxalate.

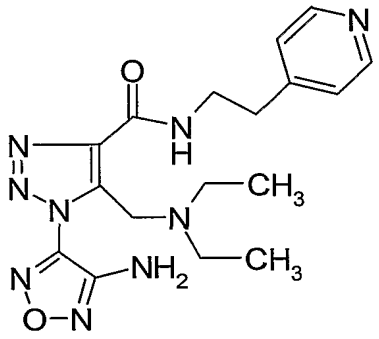


The title compound was prepared in exactly the same manner as example 14 starting from 1-(4-aminofurazan-3-yl)-5-dimethylaminomethyl-1*H*-[1,2,3]triazole-4-carboxylic acid and 4-(2-

aminoethyl)pyridine. The free base was precipitated as the dioxalate salt from acetone. Mp 190-193 °C.

Example 19 (general procedure (A), step 4)

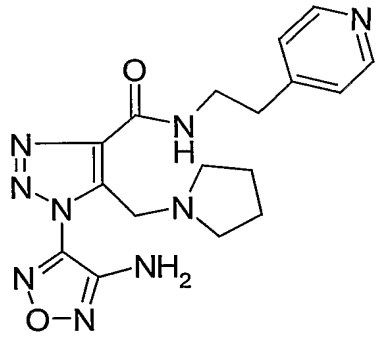
1-(4-Aminofurazan-3-yl)-5-diethylaminomethyl-1*H*-[1,2,3]triazole-4-carboxylic acid (2-pyridin-4-ylethyl)amide dioxalate.



The title compound was prepared in exactly the same manner as example 14 starting from 1-(4-aminofurazan-3-yl)-5-diethylaminomethyl-1*H*-[1,2,3]triazole-4-carboxylic acid and 4-(2-aminoethyl)pyridine. The free base was precipitated as the dioxalate salt from acetone. Mp 175-177 °C.

Example 20 (general procedure (A), step 4)

1-(4-Aminofurazan-3-yl)-5-pyrrolidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid (2-pyridin-4-ylethyl)amide dioxalate.

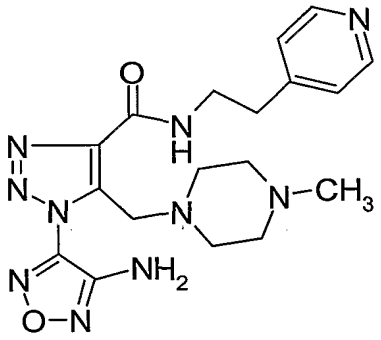


The title compound was prepared in exactly the same manner as example 14 starting from 1-(4-aminofurazan-3-yl)-5- pyrrolidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid and 4-(2-

aminoethyl)pyridine. The free base was precipitated as the dioxalate salt from acetone. Mp 185-190 °C.

Example 21 (general procedure (A), step 4)

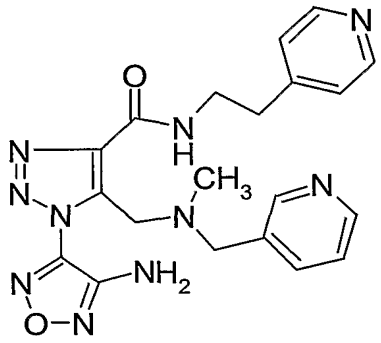
1-(4-Aminofurazan-3-yl)-5-(4-methylpiperazin-1-ylmethyl)-1*H*-[1,2,3]triazole-4-carboxylic acid (2-pyridin-4-ylethyl)amide



The title compound was prepared in exactly the same manner as example 14 starting from 1-(4-aminofurazan-3-yl)-5-(4-methylpiperazin-1-ylmethyl)-1*H*-[1,2,3]triazole-4-carboxylic acid and 4-(2-aminoethyl)pyridine. Mp 75-80 °C.

Example 22 (general procedure (A), step 4)

1-(4-Aminofurazan-3-yl)-5-[(methylpyridin-3-ylmethylamino)methyl]-1*H*-[1,2,3]triazole-4-carboxylic acid (2-pyridin-4-ylethyl)amide trioxalate.

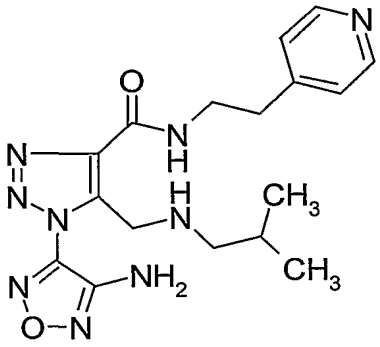


The title compound was prepared in exactly the same manner as example 14 starting from 1-(4-aminofurazan-3-yl)-5-[(methylpyridin-3-ylmethylamino)methyl]-1*H*-[1,2,3]triazole-4-

carboxylic acid and 4-(2-aminoethyl)pyridine. The free base was precipitated as the trioxalate salt from acetone. Mp >100 °C decompose.

Example 23 (general procedure (A), step 4)

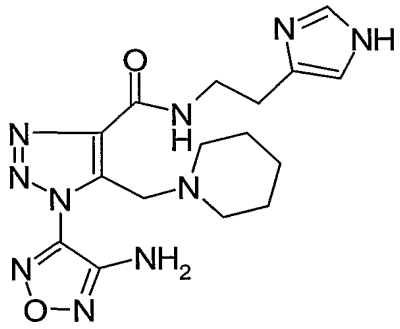
1-(4-Aminofurazan-3-yl)-5-(isobutylaminomethyl)-1*H*-[1,2,3]triazole-4-carboxylic acid (2-pyridin-4-ylethyl)amide



The title compound was prepared in exactly the same manner as example 14 starting from 1-(4-aminofurazan-3-yl)-5-(isobutylaminomethyl)-1*H*-[1,2,3]triazole-4-carboxylic acid and 4-(2-aminoethyl)pyridine. The free base was precipitated as the dioxalate salt from ethanol.

Example 24 (general procedure (A), step 4)

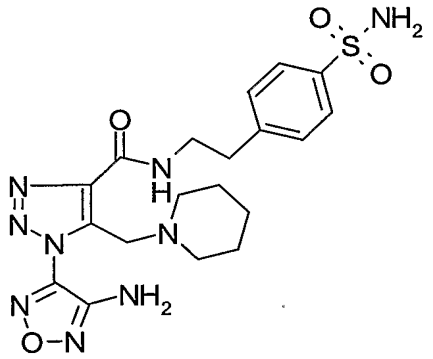
1-(4-Aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid [2-(1*H*-imidazol-4-yl)ethyl]amide



The title compound was prepared in exactly the same manner as example 14 starting from 1-(4-aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid and histamine. Mp 208-210 °C.

Example 25 (general procedure (A), step 4)

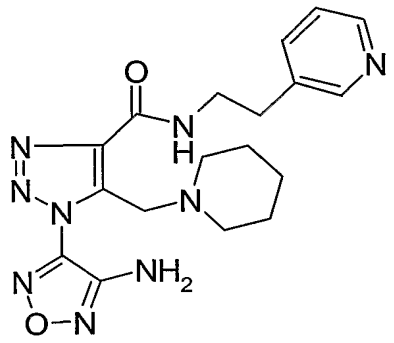
1-(4-Aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid [2-(4-sulfamoylphenyl)ethyl]amide



The title compound was prepared in exactly the same manner as example 14 starting from 1-(4-aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid and 4-(2-aminoethyl)benzenesulfonamide.

Example 26 (general procedure (A), step 4)

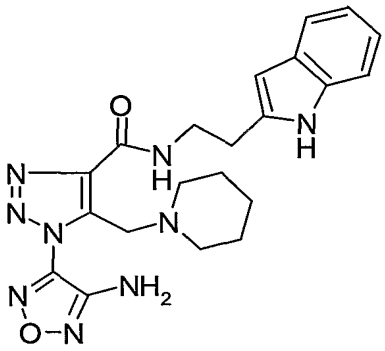
1-(4-Aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid (2-pyridin-3-ylethyl)amide



The title compound was prepared in exactly the same manner as example 14 starting from 1-(4-aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid and 3-(2-aminoethyl)pyridine. Mp 162-63 °C.

Example 27 (general procedure (A), step 4)

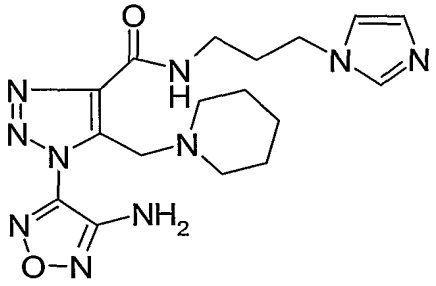
1-(4-Aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid [2-(1*H*-indol-2-yl)ethyl]amide



The title compound was prepared in exactly the same manner as example 14 starting from 1-(4-aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid and tryptamine. Mp 176-177 °C.

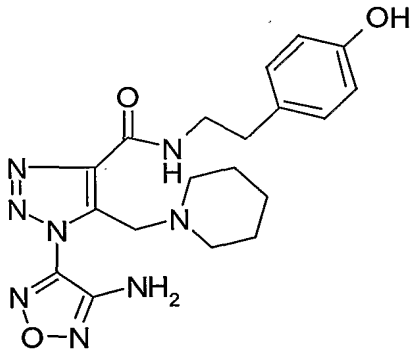
Example 28 (general procedure (A), step 4)

1-(4-Aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid (3-imidazol-1-ylpropyl)amide



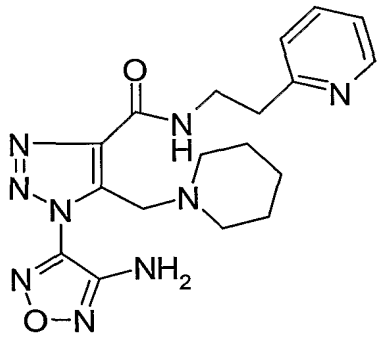
The title compound was prepared in exactly the same manner as example 14 starting from 1-(4-aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid and 1-(3-aminopropyl)imidazol. Mp 169-170 °C.

Example 29 (general procedure (A), step 4)
1-(4-Aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid [2-(4-hydroxyphenyl)ethyl]amide



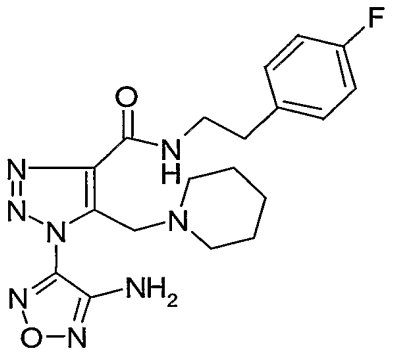
The title compound was prepared in exactly the same manner as example 14 starting from 1-(4-aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid and 4-(2-aminoethyl)phenol. Mp 142-144 °C.

Example 30 (general procedure (A), step 4)
1-(4-Aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid (2-pyridin-2-ylethyl)amide



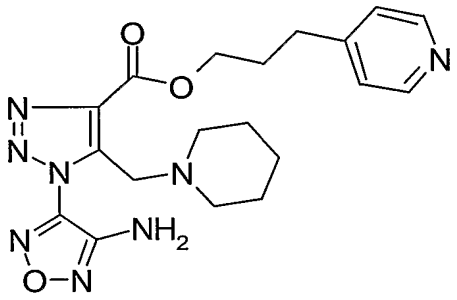
The title compound was prepared in exactly the same manner as example 14 starting from 1-(4-aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid and 2-(2-aminoethyl)pyridine. Mp 121-123 °C.

Example 31 (general procedure (A), step 4)
1-(4-Aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid [2-(4-fluorophenyl)ethyl]amide



The title compound was prepared in exactly the same manner as example 14 starting from 1-(4-aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid and 4-(2-aminoethyl)flourobenzene. Mp 191-193 °C.

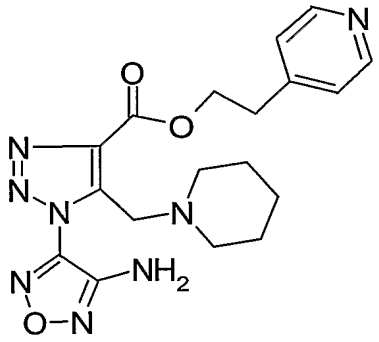
Example 32 (general procedure (A), step 6)
1-(4-Aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid 3-pyridin-4-ylpropyl ester oxalate



To a suspension of 1-(4-aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid , hydrochloride (107 mg, 0.33 mmol) in dry tetrahydrofuran, carbonyldiimidazole (67 mg, 0.41 mmol) was added. The reaction mixture was heated at reflux for 2 hours. 4-Pyridinepropanol (0.82 mmol, 112 mg was added and the reaction mixture was heated at reflux for 1 hour. After cooling to room temperature water (50 ml) was added. The water phase was extracted with ether (2 x 50 ml). The organic extracts were dried over magnesium sulphate and evaporated. The crude compound was crystallised as the oxalate salt from acetone. Yield 55 mg. Mp > 50 °C decompose.

Example 33 (general procedure (A), step 6)

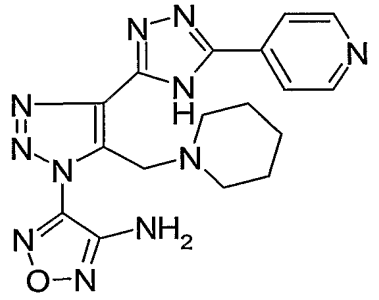
1-(4-Aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid 2-pyridin-4-ylethyl ester oxalate



The title compound was prepared in exactly the same manner as example 32 starting from 1-(4-aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid and 4-(2-hydroxyethyl)pyridine. Mp 191-193 °C.

Example 34 (general procedure (A), step 7)

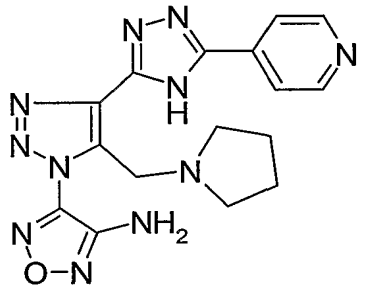
4-[5-Piperidin-1-ylmethyl-4-(5-pyridin-4-yl-4*H*-[1,2,4]triazol-3-yl)-[1,2,3]triazol-1-yl]furazan-3-ylamine dihydrochloride



To a suspension of 1-(4-aminofurazan-3-yl)-5-piperidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid , hydrochloride (990 mg, 3.0 mmol) in dry tetrahydrofuran (80 ml), triethylamine (400 mg, 4 mmol) was added and the reaction mixture was stirred at room temperature for 20 min. Carbonyldiimidazole (450 mg, 3.3 mmol) was added and the reaction mixture was heated at reflux for 1 hour. The reaction mixture was evaporated to dryness, and the crystaline mass was washed with diethyl ether. The crude compound (700 mg, 2.0 mmol) was resuspended in tetrahydrofuran (100 ml) and pyridine-4-carboxylic acid amidrazone (400 mg, 3.0 mmol, Chem. Pharm. Bull. 18(8) 1696-1698, 1970) was added. The reaction mixture was stirred at room temperature overnight and the precipitated compound was filtered and

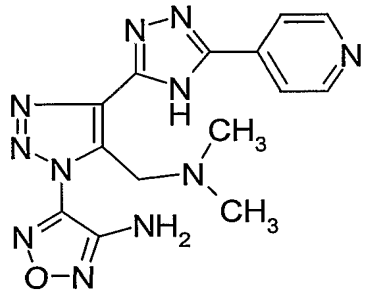
dried. The crude compound (454 mg, 1.1 mmol) was dissolved in absolute ethanol (80 ml) and the reaction mixture was heated at reflux for 6 hours. After cooling the free base of the title compound was precipitated as the dihydrochloric acid salt by the addition of hydrocloric acid to the ethanol solution. Yield 470 mg. Mp > 270 °C.

Example 35 (general procedure (A), step 7)
4-[4-(5-Pyridin-4-yl-4*H*-[1,2,4]triazol-3-yl)-5-pyrrolidin-1-ylmethyl-[1,2,3]triazol-1-yl]furazan-3-ylamine dihydrochloride



The title compound was prepared in exactly the same manner as example 34 starting from 1-(4-aminofurazan-3-yl)-5-pyrrolidin-1-ylmethyl-1*H*-[1,2,3]triazole-4-carboxylic acid.
Mp >270 °C.

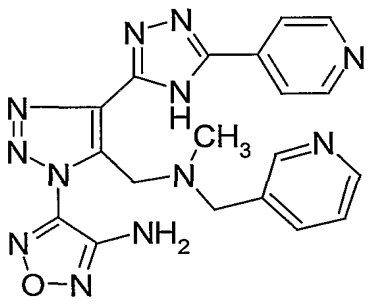
Example 36 (general procedure (A), step 7)
4-[5-Dimethylaminomethyl-4-(5-pyridin-4-yl-4*H*-[1,2,4]triazol-3-yl)-[1,2,3]triazol-1-yl]furazan-3-ylamine dihydrochloride



The title compound was prepared in exactly the same manner as example 34 starting from 1-(4-aminofurazan-3-yl)-5-dimethylaminomethyl-1*H*-[1,2,3]triazole-4-carboxylic acid. Mp 241-243 °C.

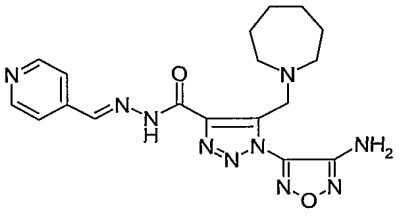
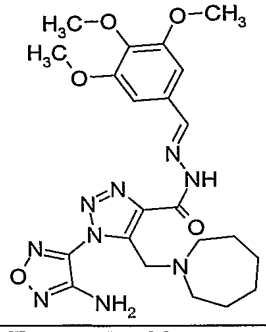
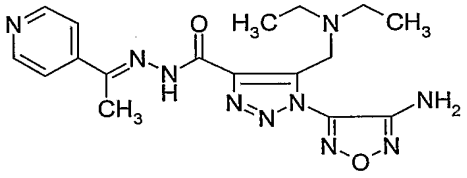
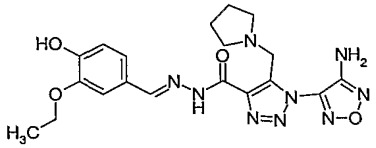
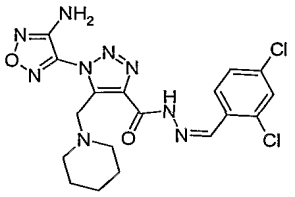
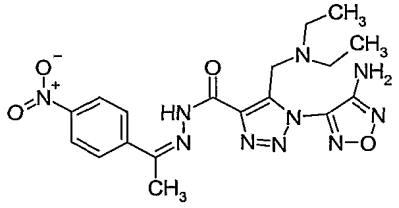
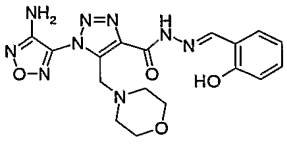
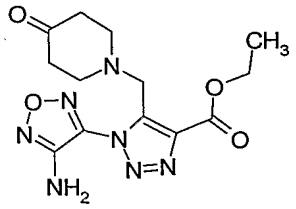
Example 37 (general procedure (A), step 7)

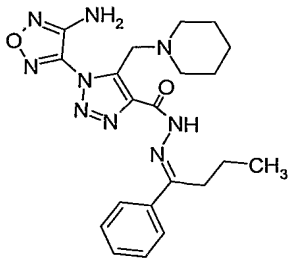
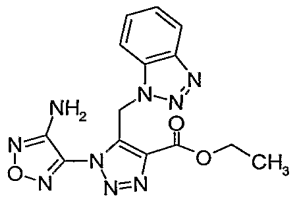
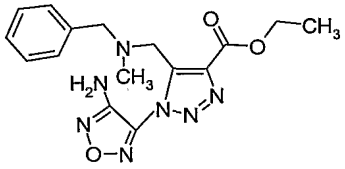
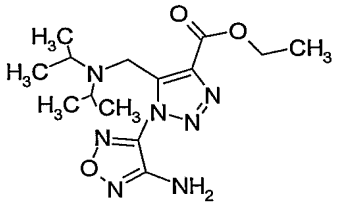
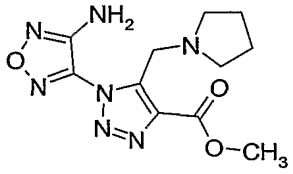
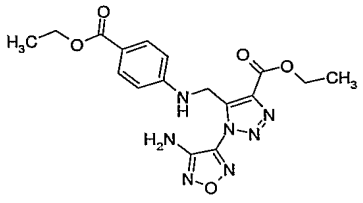
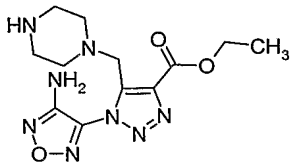
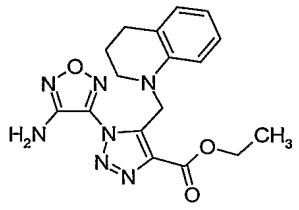
4-[5-[(Methylpyridin-3-ylmethylamino)methyl]-4-(5-pyridin-4-yl-4*H*-[1,2,4]triazol-3-yl)-[1,2,3]-triazol-1-yl]furazan-3-ylamine trihydrochloride

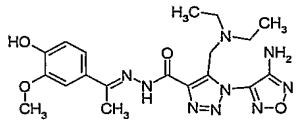
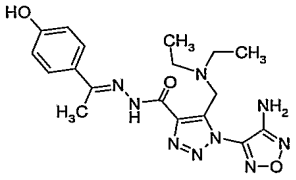
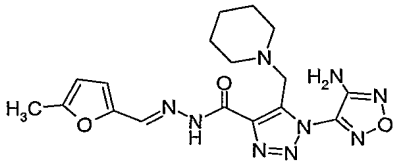
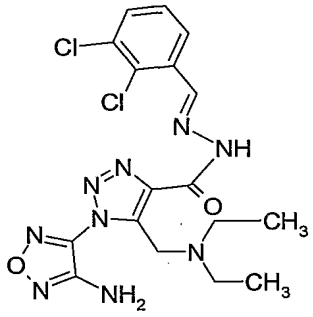
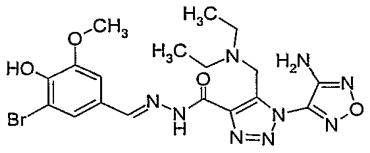
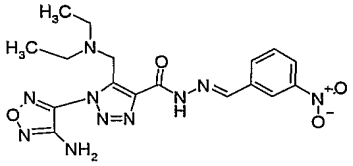
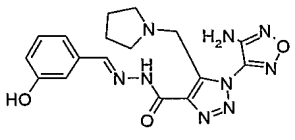
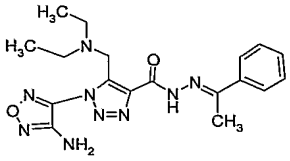


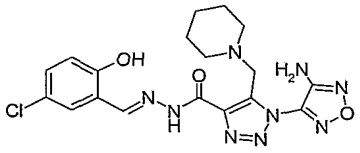
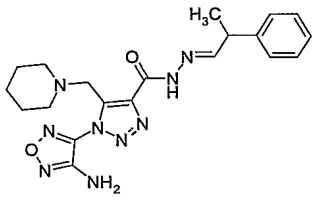
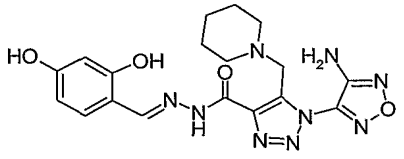
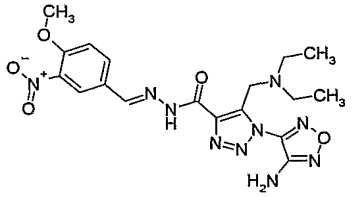
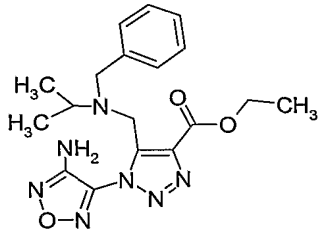
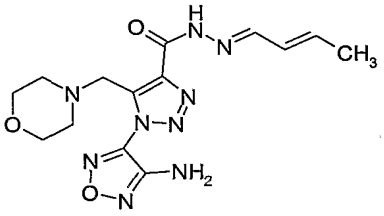
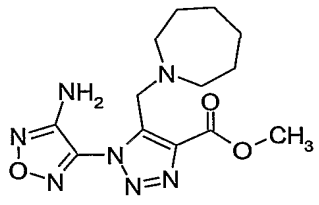
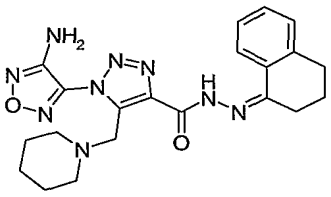
The title compound was prepared in exactly the same manner as example 34 starting from 1-(4-aminofurazan-3-yl)-5-[(methyl-pyridin-3-ylmethyl-amino)-methyl]-1*H*-[1,2,3]triazole-4-carboxylic acid. Mp 228-231 °C.

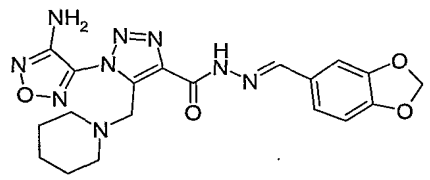
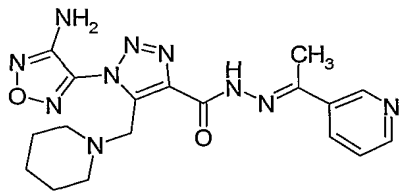
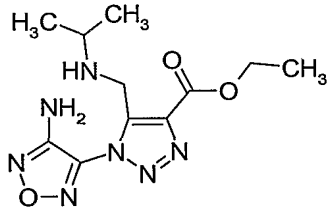
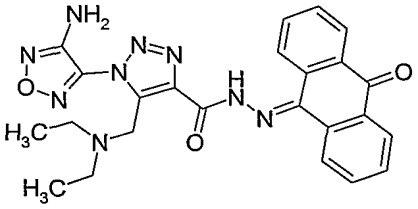
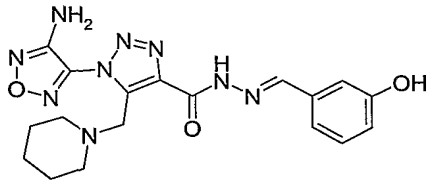
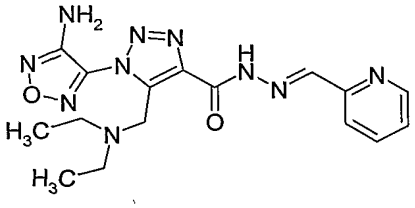
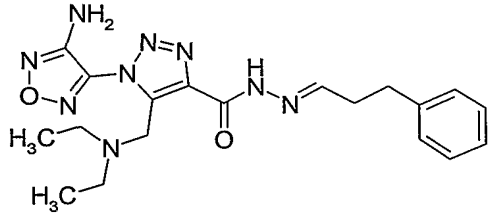
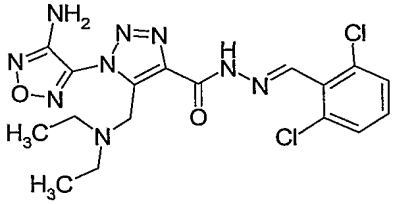
The following examples are also within the scope of the present invention. These compounds may be obtained from SPECS and BioSPECS, B. V. Fleminglaan 16, 2289 CP Rijswijk, The Netherlands:

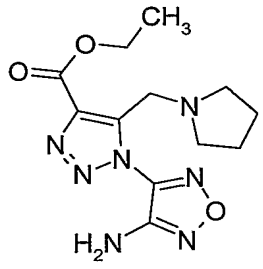
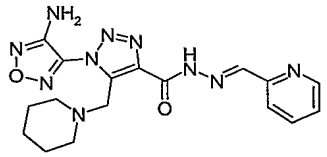
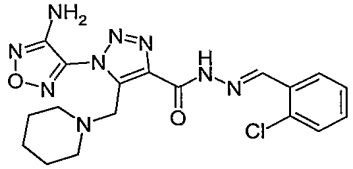
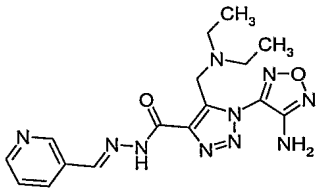
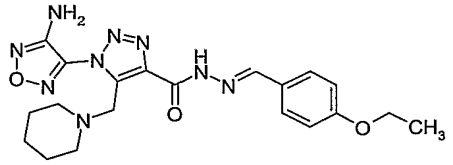
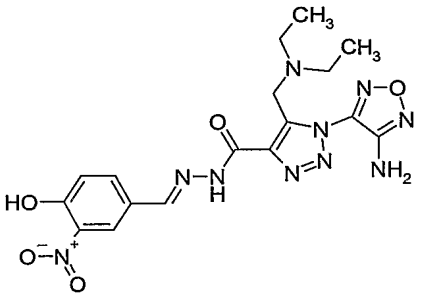
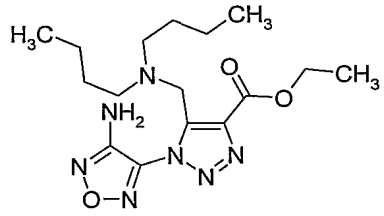
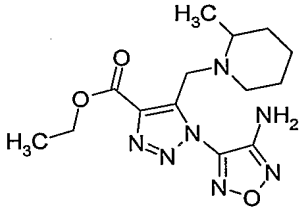
Example 38 	**Example 39** 
Example 40 	**Example 41** 
Example 42 	**Example 43** 
Example 44 	**Example 45** 

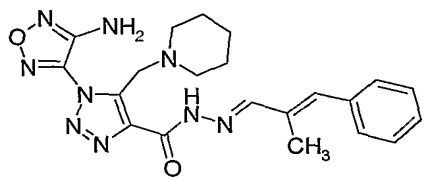
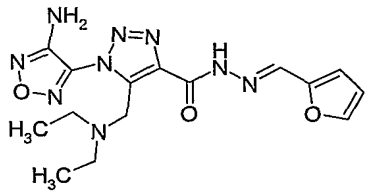
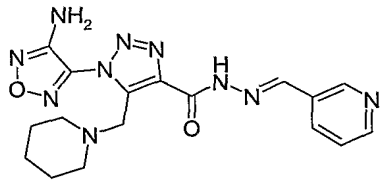
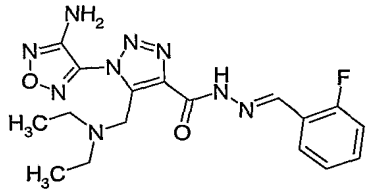
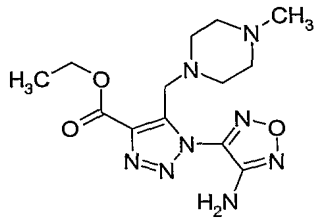
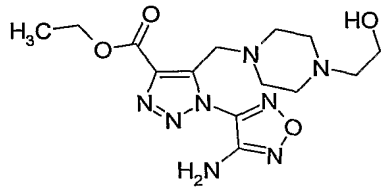
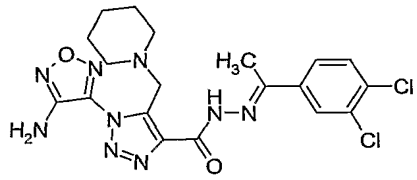
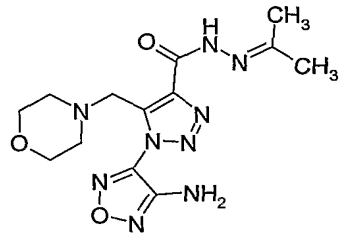
Example 46 	**Example 47** 
Example 48 	**Example 49** 
Example 50 	**Example 51** 
Example 52 	**Example 53** 

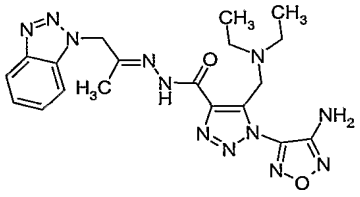
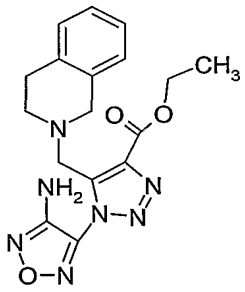
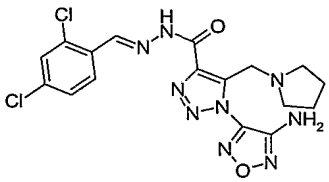
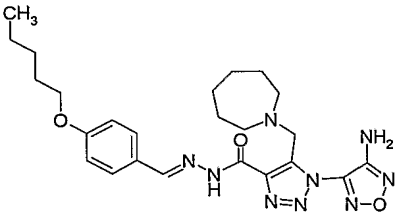
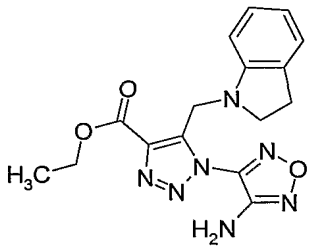
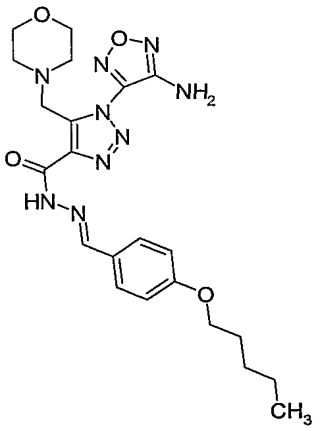
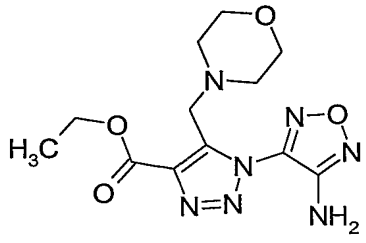
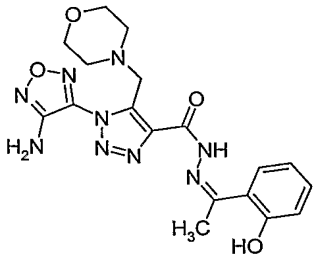
Example 54 	**Example 55** 
Example 56 	**Example 57** 
Example 58 	**Example 59** 
Example 60 	**Example 61** 

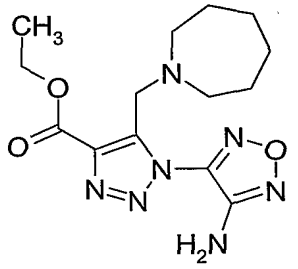
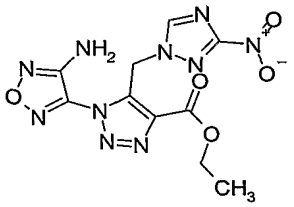
Example 62 	**Example 63** 
Example 64 	**Example 65** 
Example 66 	**Example 67** 
Example 68 	**Example 69** 

Example 70 	**Example 71** 
Example 72 	**Example 73** 
Example 74 	**Example 75** 
Example 76 	**Example 77** 

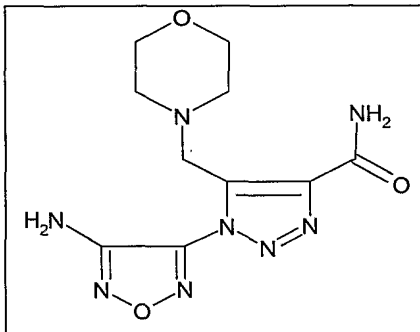
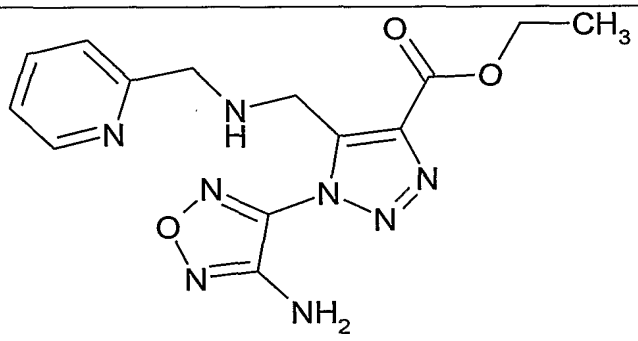
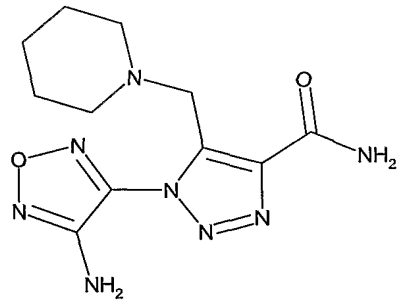
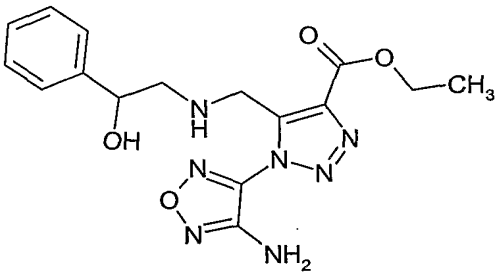
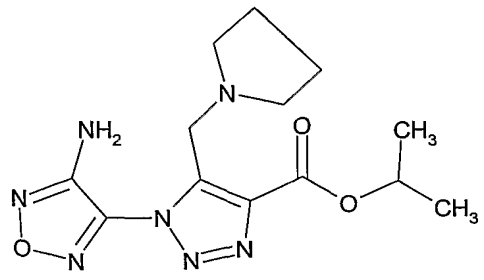
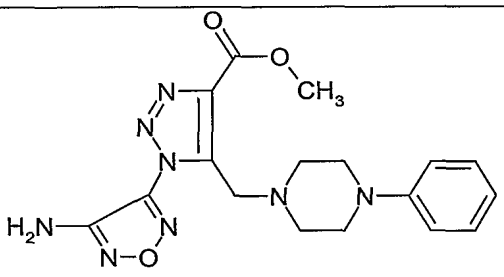
Example 78 	**Example 79** 
Example 80 	**Example 81** 
Example 82 	**Example 83** 
Example 84 	**Example 85** 

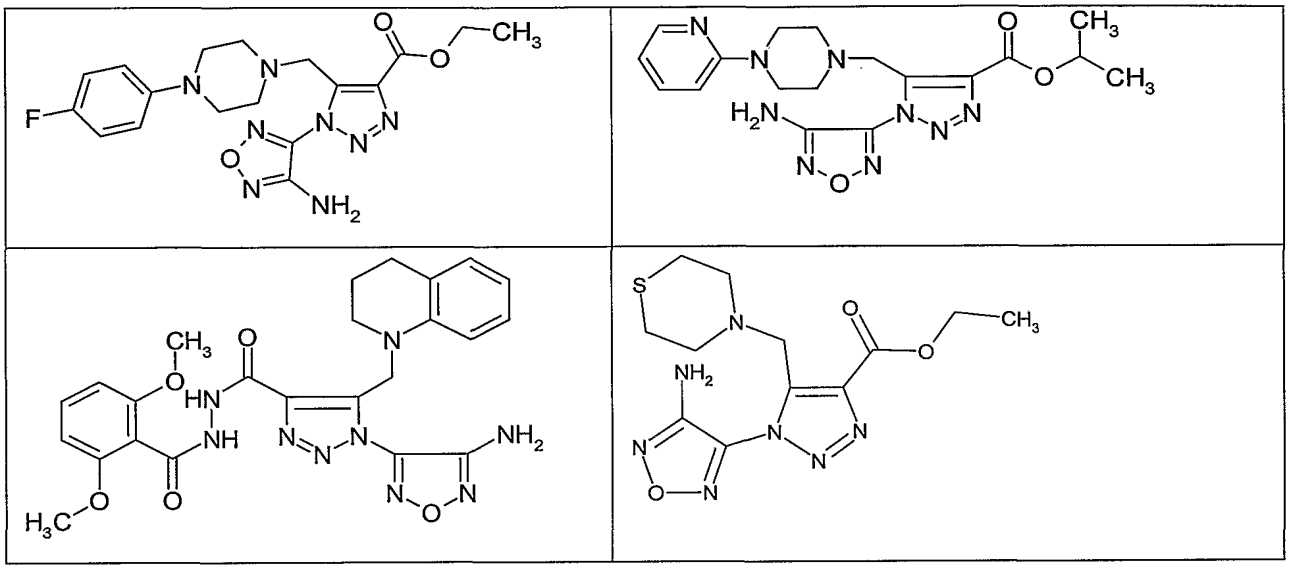
Example 86 	**Example 87** 
Example 88 	**Example 89** 
Example 90 	**Example 91** 
Example 92 	**Example 93** 

Example 94 	**Example 95** 
Example 96 	**Example 97** 
Example 98 	**Example 99** 
Example 100 	**Example 101** 

Example 102	Example 103
	

The following compounds are also comprised by the invention:



ASSAY

Inhibition of GSK-3 by a test compound was evaluated using human GSK-3β and a glycogen synthase derived substrate with the following amino acid sequence:

YRRAAVPPSPSLSRHSSPHQS(PO_4)EDEEE-NH_2.

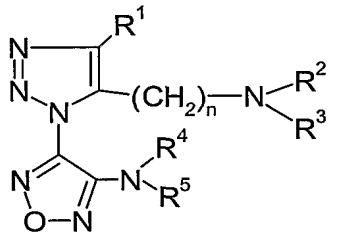
In brief, GSK-3β was incubated with 32 μM substrate and varying concentrations of test compound in a buffer containing 0.1 mM ^{33}P-labeled ATP, 10 mM magnesium acetate, 8 mM MOPS pH 7.0, 0.2 mM EDTA, 0.1% dithiothreitol and 0.03% Triton-X100 for 60 min at room temperature. The reaction was performed using 96-well filter plates. The reaction was terminated by filtration followed by addition of 25 μl 2% phosphoric acid to each well. All wells were then washed three times in 0.5% phosphoric acid to remove unreacted ^{33}P-labeled ATP, dried and radioactivity was counted in a Packard topcounter. Dose-response profiles were generated, and the IC_{50} value for inhibition of GSK-3 by the test compound was calculated using a four-parameter logistic function.

The following compounds inhibited GSK-3 with an IC_{50} value lower than 10 μM:
Examples 8, 11, 12, 14, 15, 20, 21, 27, 31, 34, 35, 36, 41, 44, 55, 60, 62, 64, 67, 70, 74 and 88.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention as defined by the appended claims.

CLAIMS

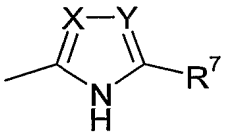
1. A pharmaceutical composition comprising, as an active ingredient, at least one compound of the general formula (I):



(I)

wherein

R^1 is –CN, -C(=O)NR^6R^7, -C(=O)NH-NR^6R^7, –C(=O)NH-N=CR^6R^7, –C(=O)OR^7, –CR^6=N-NH-C(=O)R^7 or



,

X and Y independently are =C- or =N(R^6)-,

R^6 is hydrogen or C_{1-6}-alkyl,

R^7 is hydrogen, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, aryl, heteroaryl, C_{3-8}-cycloalkyl, C_{3-8}-heterocyclyl, aryl-C_{1-6}-alkyl, heteroaryl-C_{1-6}-alkyl, heteroarylamino-C_{1-6}-alkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, C_{3-8}-heterocyclyl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, heteroaryl-C_{2-6}-alkenyl, C_{3-8}-cycloalkyl-C_{2-6}-alkenyl, C_{3-8}-heterocyclyl-C_{2-6}-alkenyl, aryl-C_{2-6}-alkynyl, heteroaryl-C_{2-6}-alkynyl, C_{3-8}-cycloalkyl-C_{2-6}-alkynyl or C_{3-8}-heterocyclyl-C_{2-6}-alkynyl,

- wherein the cyclic moieties optionally may be substituted with one to three substituents independently selected from halogen, nitro, cyano, oxo, trifluoromethyl, hydroxy, C_{1-6}-alkoxy, carboxy, C_{1-6}-alkoxycarbonyl, C_{1-6}-alkyl, –NR^8R^9, -S-C_{1-6}-alkyl, -S(=O)-C_{1-6}-alkyl, -$S(=O)_2$-C_{1-6}-alkyl and -$S(=O)_2NR^8R^9$, wherein R^8 and R^9 independently are hydrogen or C_{1-6}-alkyl, or with two substituents in adjacent positions together forming a –O-$(CH_2)_m$-O- radical, wherein m is 1 or 2,

or R^6 and R^7, when attached to the same carbon atom, together with the said carbon atom may form a mono-, bi- or tricyclic, 3 to 14 membered ring system, which is optionally substituted with one to three substituents independently selected from halogen, nitro, cyano, oxo, trifluoromethyl, hydroxy, C_{1-6}-alkoxy, carboxy, C_{1-6}-alkoxycarbonyl, C_{1-6}-alkyl, $-NR^8R^9$, $-S-C_{1-6}$-alkyl, $-S(=O)-C_{1-6}$-alkyl, $-S(=O)_2-C_{1-6}$-alkyl and $-S(=O)_2NR^8R^9$, wherein R^8 and R^9 independently are hydrogen or C_{1-6}-alkyl,

n is 1 or 2,

R^2 and R^3 independently are hydrogen, C_{1-6}-alkyl, aryl, heteroaryl, aryl-C_{1-6}-alkyl or heteroaryl-C_{1-6}-alkyl, or R^2 and R^3 together with the nitrogen atom to which they are attached form a 3 to 7 membered, heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur, which ring may optionally be annelated with aryl or heteroaryl,

- wherein the cyclic moieties optionally may be substituted with one to three substituents independently selected from halogen, nitro, cyano, oxo, trifluoromethyl, hydroxy, C_{1-6}-alkoxy, carboxy, C_{1-6}-alkoxycarbonyl, C_{1-6}-alkyl, C_{1-6}-alkyl substituted with hydroxy, $-NR^{10}R^{11}$, $-S-C_{1-6}$-alkyl, $-S(=O)-C_{1-6}$-alkyl, $-S(=O)_2-C_{1-6}$-alkyl and $-S(=O)_2NR^{10}R^{11}$, wherein R^{10} and R^{11} independently are hydrogen or C_{1-6}-alkyl, and

R^4 and R^5 independently are hydrogen or C_{1-6}-alkyl, or R^4 and R^5 together with the nitrogen atom to which they are attached form a 3 to 7 membered, heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulfur,

as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof,

together with one or more pharmaceutically acceptable carriers or excipients.

2. A pharmaceutical composition according to claim 1, wherein R^1 is $-C(=O)NH-N=CR^6R^7$, wherein R^6 is as defined in claim 1, and R^7 is C_{1-6}-alkyl, C_{2-6}-alkenyl, aryl, aryl-C_{1-6}-alkyl, aryl-C_{2-6}-alkenyl, heteroaryl or heteroaryl-C_{1-6}-alkyl, wherein the cyclic moieties may optionally be substituted as defined in claim 1.

3. A pharmaceutical composition according to claim 2, wherein R^7 is pyridyl, 1-benzotriazolyl-methyl, phenyl or furanyl, which may optionally be substituted with one to three substituents selected from C_{1-6}-alkoxy, hydroxy, C_{1-6}-alkyl, halogen and nitro or with two substituents in adjacent positions together forming a $-O-(CH_2)_m-O-$ radical, wherein m is 1 or 2.

4. A pharmaceutical composition according to claim 2, wherein R^7 is pyridyl.

5. A pharmaceutical composition according to claim 2, wherein R^7 is phenyl, which may optionally be substituted with one to three substituents selected from C_{1-6}-alkoxy, hydroxy, C_{1-6}-alkyl, halogen and nitro or with two substituents in adjacent positions together forming a $-O-(CH_2)_m-O-$ radical, wherein m is 1 or 2.

6. A pharmaceutical composition according to claim 1, wherein R^1 is $-C(=O)NH-N=CR^6R^7$, wherein R^6 and R^7 together form 1,2,3,4-tetrahydronaphthyl or 9,10-dihydroanthracenyl, which may optionally be substituted with one to three substituents selected from C_{1-6}-alkoxy, hydroxy, oxo, C_{1-6}-alkyl, halogen and nitro.

7. A pharmaceutical composition according to claim 1, wherein R^1 is $-C(=O)OR^7$, wherein R^7 is hydrogen, C_{1-6}-alkyl or heteroaryl-C_{1-6}-alkyl, wherein the heteroaryl moiety may optionally be substituted as defined in claim 1.

8. A pharmaceutical composition according to claim 1, wherein R^1 is $-C(=O)OR^7$, wherein R^7 is C_{1-6}-alkyl or pyridyl-C_{1-6}-alkyl.

9. A pharmaceutical composition according to claim 1, wherein R^1 is $-C(=O)NR^6R^7$, wherein R^6 and R^7 are as defined in claim 1.

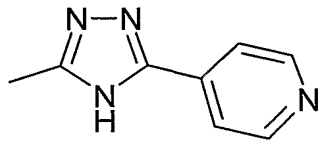
10. A pharmaceutical composition according to claim 9, wherein R^6 is as defined in claim 1, and R^7 is heteroaryl-C_{1-6}-alkyl, heteroarylamino-C_{1-6}-alkyl or aryl-C_{1-6}-alkyl, which may optionally be substituted as defined in claim 1.

11. A pharmaceutical composition according to claim 10, wherein R^6 is as defined in claim 1, and R^7 is pyridyl-C_{1-6}-alkyl, imidazolyl-C_{1-6}-alkyl, indolyl-C_{1-6}-alkyl, pyridylamino-C_{1-6}-alkyl or phenyl-C_{1-6}-alkyl, which may optionally be substituted as defined in claim 1.

12. A pharmaceutical composition according to claim 11, wherein R^6 is as defined in claim 1, and R^7 is pyridyl-C_{1-6}-alkyl, imidazolyl-C_{1-6}-alkyl, indolyl-C_{1-6}-alkyl, pyridylamino-C_{1-6}-alkyl or phenyl-C_{1-6}-alkyl, wherein the cyclic moieties may optionally be substituted with one to three substituents selected from halogen, nitro, hydroxy, and $-S(=O)_2NH_2$.

13. A pharmaceutical composition according to claim 1, wherein R^1 is $-C(=O)-NH-NH_2$.

14. A pharmaceutical composition according to claim 1, wherein R^1 is



.

15. A pharmaceutical composition according to any one of the preceding claims, wherein n is 1.

16. A pharmaceutical composition according to any one of the preceding claims 1 to 15, wherein R^2 and R^3 independently are selected from hydrogen, C_{1-6}-alkyl, aryl-C_{1-6}-alkyl, aryl, heteroaryl-C_{1-6}-alkyl and C_{3-8}-cycloalkyl, wherein the cyclic moieties may optionally be substituted as defined in claim 1.

17. A pharmaceutical composition according to claim 16, wherein R^2 and R^3 independently are selected from hydrogen, C_{1-6}-alkyl, phenyl-C_{1-6}-alkyl, phenyl, pyridyl-C_{1-6}-alkyl and C_{3-8}-cycloalkyl, wherein the cyclic moieties optionally may be substituted with one to three substituents selected from C_{1-6}-alkyl, oxo, nitro, C_{1-6}-alkoxycarbonyl and C_{1-6}-alkyl substituted with hydroxy.

18. A pharmaceutical composition according to claim 17, wherein R^2 and R^3 are both C_{1-6}-alkyl.

19. A pharmaceutical composition according to any one of the preceding claims 1 to 15, wherein R^2 and R^3 together with the nitrogen atom to which they are attached form a ring system selected from 1-perhydroazepinyl, 1-piperidinyl, 1-morpholinyl, 1,2,3,4-tetrahydroquinolin-1-yl, 1-pyrrolidinyl, 1-piperazinyl, 2,3-dihydroindol-1-yl, 1-benzotriazol-1-yl, 1,2,3,4-

tetrahydroisoquinolin-2-yl and 1,2,4-triazol-1-yl, which may optionally be substituted as defined in claim 1.

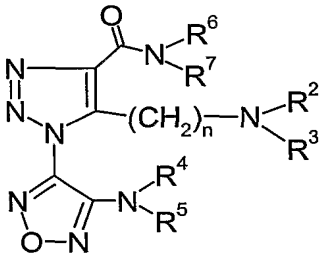
20. A pharmaceutical composition according to claim 19, wherein R^2 and R^3 together with the nitrogen atom to which they are attached form a ring system selected from 1-perhydroazepinyl, 1-piperidinyl, 1-pyrrolidinyl and 1-morpholinyl, which may optionally be substituted with one to three substituents selected from C_{1-6}-alkyl, oxo, nitro, C_{1-6}-alkoxycarbonyl and C_{1-6}-alkyl substituted with hydroxy.

21. A pharmaceutical composition according to claim 20, wherein R^2 and R^3 together with the nitrogen atom to which they are attached form a ring selected from 1-perhydroazepinyl, 1-piperidinyl, 1-pyrrolidinyl and 1-morpholinyl.

22. A pharmaceutical composition according to any one of the preceding claims, wherein R^4 and R^5 are both hydrogen.

23. A pharmaceutical composition in unit dosage form, comprising from about 0.05 mg to about 1000 mg, preferably from about 0.1 mg to about 500 mg and especially preferred from about 0.5 mg to about 200 mg of the compound of the general formula (I) as defined in any one of the claims 1 to 22 or an optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

24. A compound of the general formula (I'):



(I')

wherein n and R^2 to R^7 are as defined in any one of the claims 1 or 9 to 22,
as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

25. Use of a compound of the general formula (I) as defined in any one of the claims 1 to 22 as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for the treatment and/or delaying or prevention of the progression of diseases, disorders and conditions, wherein an inhibition of GSK-3 is beneficial.

26. Use of a compound of the general formula (I) as defined in any one of the claims 1 to 22 as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for the treatment and/or delaying or prevention of the progression of diseases, disorders and conditions related to GSK-3.

27. Use of a compound of the general formula (I) as defined in any one of the claims 1 to 22 as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for the treatment and/or delaying or prevention of the progression of diseases, disorders and conditions, wherein growth factor induced inhibition of GSK-3 is insufficient.

28. Use of a compound of the general formula (I) as defined in any one of the claims 1 to 22 as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for the treatment and/or delaying or prevention of the progression of diseases, disorders and conditions, wherein glycogen metabolism exhibits abnormalities.

29. Use of a compound of the general formula (I) as defined in any one of the claims 1 to 22 as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for the treatment and/or delaying or prevention of the progression of diseases, disorders and conditions, wherein glycogen synthase is insufficiently activated.

30. Use of a compound of the general formula (I) as defined in any one of the claims 1 to 22 as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for the lowering of blood glucose.

31. Use of a compound of the general formula (I) as defined in any one of the claims 1 to 22 as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for the treatment and/or delaying or prevention of the progression of diseases, disorders and conditions involving elevated blood glucose.

32. Use of a compound of the general formula (I) as defined in any one of the claims 1 to 22 as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for the treatment and/or delaying or prevention of the progression of hyperglycemia.

33. Use of a compound of the general formula (I) as defined in any one of the claims 1 to 22 as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for the treatment and/or delaying or prevention of the progression of IGT.

34. Use of a compound of the general formula (I) as defined in any one of the claims 1 to 22 as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for the treatment and/or delaying or prevention of the progression of Type 2 diabetes.

35. Use of a compound of the general formula (I) as defined in any one of the claims 1 to 22 as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from IGT to Type 2 diabetes.

36. Use of a compound of the general formula (I) as defined in any one of the claims 1 to 22 as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for the delaying or prevention of the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes.

37. Use of a compound of the general formula (I) as defined in any one of the claims 1 to 22 as well as any optical or geometric isomer or tautomeric form thereof including mixtures of

these or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for the treatment and/or delaying or prevention of the progression of Type 1 diabetes.

38. Use according to any one of the preceding claims 25 to 37 in combination with one or more further antidiabetic agents.

39. Use according to any one of the preceding claims 25 to 38 n combination with one or more antiobesity agents.

40. Use according to any one of the preceding claims 25 to 39 in combination with one or more antihypertensive agents.

41. Use of a compound of the general formula (I) as defined in any one of the claims 1 to 22 as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for the treatment and/or prevention of Alzheimer's disease.

42. Use according to claim 41 in combination with one or more agents for the treatment of Alzheimer's disease.

43. Use of a compound of the general formula (I) as defined in any one of the claims 1 to 22 as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof for the preparation of a pharmaceutical composition for the treatment and/or prevention of bipolar disorder.

44. Use according to claim 43 in combination with one or more agents for the treatment of bipolar disorder.

45. A method for the treatment and/or prevention of diseases and disorders, wherein an inhibition of GSK-3 is beneficial the method comprising administering to a subject in need thereof an effective amount of a compound of the general formula (I) as defined in any one of the claims 1 to 22 as well as any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof.

46. The method according to claim 45, wherein the effective amount of the compound of the general formula (I) is in the range of from about 0.05 mg to about 2000 mg, preferably from about 0.1 mg to about 1000 mg and especially preferred from about 0.5 mg to about 500 mg per day.

INTERNATIONAL SEARCH REPORT

I	ıal Application No
	PCT/DK 01/00676

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D413/04 C07D413/14 A61K31/4192 A61K31/4245 A61K31/443
A61K31/4439 A61K31/496 A61K31/5355 A61K31/55 A61P3/10
A61P25/18 A61P25/24 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, EMBASE, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE STN INTERNATIONAL [Online] file CHEMCATS, Screening collection; Accession no. 2001:1586603, 28 March 2000 (2000-03-28) "RN 312497-11-3" XP002902273 abstract --- DATABASE STN INTERNATIONAL [Online] file CHEMCATS, Chem. Div. Inc. Product Library; Accession no. 2001:815071, 26 April 2001 (2001-04-26) "RN 296792-97-7" XP002902274 abstract --- -/--	24 24
P,X		

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 January 2002	15. 03. 2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Per Renström

INTERNATIONAL SEARCH REPORT

In ional Application No
PCT/DK 01/00676

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 16528 A (CHIRON CORP) 23 April 1998 (1998-04-23) the whole document ---	1-46
A	WO 99 65897 A (CHIRON CORP (US)) 23 December 1999 (1999-12-23) the whole document -----	1-46

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 01/00676

Box I ***Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)***

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 45,46
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 45,46

Claims 45,46 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1 (iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In nal Application No
PCT/DK 01/00676

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9816528 A	23-04-1998	AU 4920397 A	11-05-1998
		WO 9816528 A1	23-04-1998
		US 6153618 A	28-11-2000
WO 9965897 A	23-12-1999	AU 4956699 A	05-01-2000
		CN 1312807 T	12-09-2001
		EP 1087963 A1	04-04-2001
		WO 9965897 A1	23-12-1999